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Substituted Indole-5-carboxamides and -acetamides as Potent Nonpeptide GnRH Receptor Antagonists

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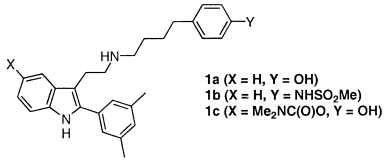
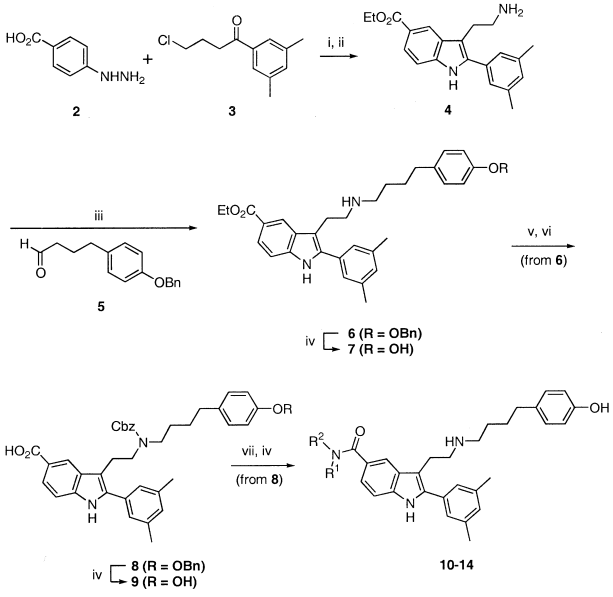
Abstract—The 2-aryltryptamine class of GnRH receptor antagonists has been modified to incorporate carboxamide and acetamide substituents at the indole 5-position. With either a phenol or methanesulfonamide terminus on the *N*-aralkyl side chain, potent binding affinity to the GnRH receptor was achieved. A functional assay for GnRH antagonism was even more sensitive to structural modification and revealed a strong preference for branched tertiary amides.

The gonadotropin-releasing hormone (GnRH; also known as luteinizing hormone-releasing hormone, or LHRH) receptor is an attractive target for pharmacological suppression of sex hormone levels.[1] GnRH agonists, which, upon chronic administration, down-regulate the receptor and desensitize the pituitary to GnRH stimulation, have been valuable agents in the treatment of such conditions as hormone-dependent cancers, endometriosis, and uterine fibroids, as well as in assisted reproduction.[1,2] More recently, peptide GnRH antagonists, which avoid the initial 'flare-up' problem, have achieved clinical success.[1,3] The first nonpeptide GnRH antagonists, offering the possibility of oral bioavailability, have recently been described in three heterocyclic series: thieno[2,3-*b*]pyridin-4-ones,[4] quinolones,[5] and indoles.[6] Indole GnRH antagonists reported from these laboratories include **1a**–**c**.[6] In the present investigation we have further explored substituents at the indole 5-position.



The first series of compounds (indole-5-carboxylates and-carboxamides bearing phenol end groups) was prepared according to Scheme 1. Heating 4-hydrazinobenzoic acid (**2**) with the 3-chloropropyl ketone **3**[7] in ethanol yielded, after complete esterification, the tryptamine derivative **4**. (See below for further discussion of this reaction.) To prepare the 'right-hand' side chain, reductive amination of aldehyde **5**[6a] by **4** gave the secondary amine **6**. The use of anhydrous magnesium sulfate (5 equiv) promoted formation of the imine, which was



Scheme 1. Conditions: (i) EtOH, Δ; (ii) cat. H_2SO_4, EtOH, Δ; (iii) (a) $MgSO_4$, $CDCl_3$, −5 to −10 °C; (b) $NaBH_4$, MeOH, −5 °C; (iv) H_2, $Pd(OH)_2/C$, EtOH–EtOAc, AcOH; (v) Cbz-Cl, *i*-Pr_2NEt, CH_2Cl_2–THF, −78 °C; (vi) (a) KOH, MeOH–H_2O, Δ; (b) H^+; (vii) R^1R^2NH, PyBOP, Et_3N, CH_2Cl_2.

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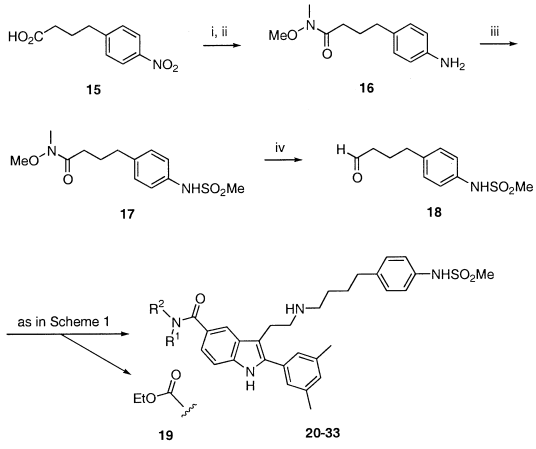
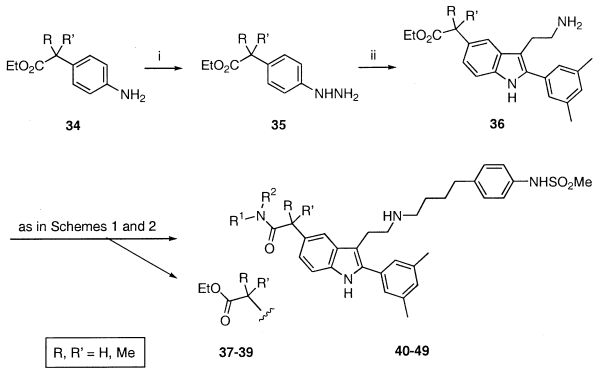
reduced in situ by sodium borohydride. Debenzylation of **6** by catalytic hydrogenation afforded **7**. For further elaboration, **6** was converted to its Cbz derivative and then saponified to give the acid **8**. Full deprotection by hydrogenolysis yielded **9**. Amide derivatives **10**–**14** were obtained by coupling **8** with amines in the presence of PyBOP reagent, followed by hydrogenation.

The second series of compounds (Scheme 2) was similar, except that the phenolic OH, a possible metabolic and toxicological liability, was replaced by methanesulfonamide. Conversion of acid **15** to its Weinreb amide followed by hydrogenation of the nitro group yielded **16**. Treatment with methanesulfonyl chloride in pyridine afforded **17**, which was reduced to aldehyde **18**. Further transformation to compounds **19**–**33** was conducted as described for Scheme 1.

For the derivatives containing homologated ester or amide substituents at the indole 5-position (Scheme 3), (4-aminophenylacetate) esters **34**[8] were converted to the hydrazines **35** by diazotization followed by stannous chloride reduction. Reaction of **35** with chloroketone **3** as in Scheme 1 afforded the tryptamines **36**. Further transformations according to the conditions of Schemes 1 and 2 yielded final products **37**–**49**.



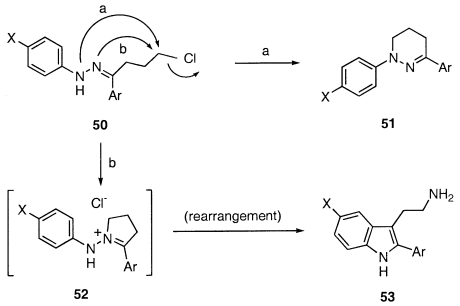
Scheme 2. Conditions: (i) MeONHMe·HCl, BOP, Et_3N, CH_2Cl_2; (ii) H_2, $Pd(OH)_2/C$, EtOH; (iii) $MeSO_2Cl$, pyridine; (iv) $LiAlH_4$, THF, 0 °C.



Scheme 3. Conditions: (i) (a) $NaNO_2$, HCl, H_2O; (b) $SnCl_2$, concd HCl; (c) Na_2CO_3; (ii) **3**, EtOH, Δ.

The preparation of tryptamines by reaction of arylhydrazines with **3** merits further comment. This variation of the Fischer indole synthesis has been extensively studied by Grandberg.[9] Although the reaction was well documented for γ-chloro aldehydes and aliphatic ketones, it was reported[9,10] that reaction of phenylhydrazine with 3-chloropropyl phenyl ketone yielded only a tetrahydropyridazine product, not the tryptamine. We have confirmed a finding from these laboratories[11] that tryptamine products can indeed be isolated from the reaction of arylhydrazones with **3**. Although the tetrahydropyridazine byproduct always appears to predominate, it is readily separable. The initially formed hydrazone **50** can cyclize by either of two pathways (Scheme 4). Depending on which of the hydrazone nitrogen atoms displaces the chloro group, ring closure can proceed via path a to the six-membered tetrahydropyridazine **51** or via path b to a five-membered ring intermediate **52**. The latter, as proposed by Grandberg[9] in related cases, can undergo a rearrangement leading to the tryptamine **53**. Our observations suggest that the relative proportions of **51** and **53** depend, in part, on the electronic character of the substituent X. Electron-withdrawing substituents might be expected to preferentially deactivate the nitrogen adjacent to the aryl group, thus disfavoring path a relative to path b. For example, tryptamine **4** (X = EtO_2C) was obtained in 29% yield, whereas yields of **40**, in which the ester is removed by one carbon atom from the aromatic ring, ranged from 11–16%. (For X = NO_2, yields of up to 40% for **53** have been obtained by this route[11]).

The compounds of this investigation were evaluated for the ability to compete with [^{125}I]-buserelin (a GnRH receptor agonist) for binding to the rat GnRH receptor.[5b] It eventually became apparent that, in the absence of bovine serum albumin (BSA) (Protocol A), the test compounds adhered significantly to the binding assay tubes, thus reducing the available concentration in solution. Because this effect was proportionally greater at low compound concentration, the resulting artificial elevation of IC_{50} levels became more of a concern as potency increased. The addition of 0.1% BSA to the assay mixture (Protocol B) mitigated this nonspecific interaction, possibly by neutralizing charges on the surface of the glass tubes. Consequently, we regard the IC_{50} determinations using Protocol B as a more accurate indication of receptor binding affinity. Results from



Scheme 4. Postulated mechanism of formation of tryptamines and tetrahydropyridazines.

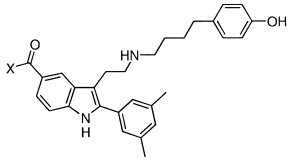
both sets of assay conditions are provided in order to facilitate comparisons within each series. In addition, most compounds were tested in a functional assay that measured inhibition of GnRH-stimulated LH release from rat primary pituitary cells.[5b]

In the first series of compounds bearing a phenolic terminus (Table 1), an ethyl ester at the indole-5-position (**7**) was well tolerated, but hydrolysis to the free acid (**9**) led to a 20-fold loss of binding affinity. Carboxamides, however, proved to be most propitious, particularly those derived from secondary amines (**10**, **11**, **13**, and **14**), which were approximately 10-fold more potent than the parent analogue **1a**. The dimethyl amide **10** also compared favorably with the similarly substituted carbamate **1c**. The only amide derived from a primary amine (**12**) was less effective. In the LH release assay, the amides showed significant inhibitory activity, whereas the parent **1a** was essentially inactive. Here the most potent compound in the series was the diisobutyl amide **14**.

When the phenol terminus was replaced by methanesulfonamide (Table 2), similar trends were observed. Again, tertiary amides were preferred. Although the differences in binding affinity were not large, activity trends were revealed in the functional assay. Most effective in blocking LH release from pituitary cells were the amides derived from certain branched, acyclic or cyclic secondary amines (**27**, **28**, and **32**).

The third set of compounds (Table 3) also contained the methanesulfonamide end group but had a one-carbon spacer between the indole 5-position and the ester or amide carbonyl group. Although no clear trends were evident in the binding assay, some structure–activity relationships were apparent in the LH release assay. Among the esters (**37**–**39**), increasing the substitution on the spacer atom markedly improved potency, from 2000 nM in the parent acetate **37** to 150 nM in the *gem*-dimethyl derivative **39**. To a lesser extent, a similar trend held true for the amides (**44** vs **40**, **45** vs **41**, and **49** vs **42**). Several medium-sized tertiary amides in the *gem*-dimethyl series (**45**–**49**) were relatively potent inhibitors of GnRH-induced LH release (IC_{50} values < 100 nM). In the case of the 5-carboxamides (Table 2), the 2,5-dimethylpyrrolidine amide **32** was 5-fold more potent in blocking LH release than the corresponding unsubstituted pyrrolidine derivative **29**. For the *gem*-dimethyl-substituted acetamides, however, the unsubstituted pyrrolidine derivative **48** was at least as active as the 2,5-dimethylpyrrolidine **49**.

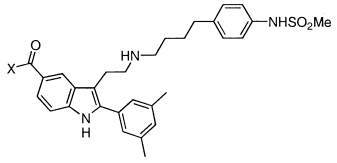
Table 1. Inhibition of GnRH receptor binding and LH release by indole-5-carboxylates/carboxamides with phenol end groups



Compd	X	rGnRH IC_{50}, nM[a]		LH Release IC_{50}, nM[b]
		Protocol A[c]	Protocol B[d]	
1a[e]	[H][f]	50		> 6200
1c[g]	[$Me_2NC(O)O$][f]	3		
7	EtO	32		
9	HO	600		
10	Me_2N	5		820
11	Et_2N	6	0.5	540
12	$PhCH_2NH$	24		
13		4		800
14	*i*-Bu_2N		5.7[h]	380

[a]Inhibition of binding of [^{125}I]-buserelin to rat pituitary GnRH receptor.
[b]Inhibition of GnRH-stimulated LH release from rat pituitary cells.
[c]Absence of BSA.
[d]Presence of 0.1% BSA.
[e]Ref 6a.
[f]Substituent in place of XCO- at indole 5-position.
[g]Ref 6b.
[h]Inhibition of binding to *human* GnRH receptor.

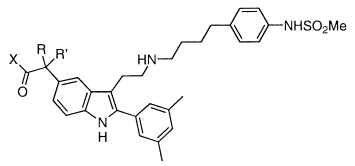
Table 2. Inhibition of GnRH receptor binding and LH release by indole-5-carboxylates/carboxamides with methanesulfonamide end groups



Compd	X	rGnRH IC_{50}, nM[a]		LH Release IC_{50}, nM[b]
		Protocol A[c]	Protocol B[d]	
1b[e]	[H][f]	7		
19	EtO	14		> 6200
20	Me_2N	2		690
21	Et_2N	2	0.2	270
22	EtNH	6		2400
23	*n*-BuN(Et)	4		240
24	*i*-PrN(Et)	3		120
25	*t*-BuN(Et)		0.8	660
26	*n*-Pr_2N	5		140
27	*i*-Pr_2N	3	0.3	72
28	*i*-Bu_2N		0.4	32
29		4	0.2	510
30		2		220
31		2	0.2	400
32		3	0.2	95
33		3	0.4	210

[a]Inhibition of binding of [^{125}I]-buserelin to rat pituitary GnRH receptor.
[b]Inhibition of GnRH-stimulated LH release from rat pituitary cells.
[c]Absence of BSA.
[d]Presence of 0.1% BSA.
[e]Ref 6c.
[f]Substituent in place of XCO- at indole 5-position.

Table 3. Inhibition of GnRH receptor binding and LH release by indole-5-acetates/acetamides with methanesulfonamide end groups



Compd	R	R′	X	rGnRH IC_{50}, nM[a]		LH Release IC_{50}, nM[b]
				Protocol A[c]	Protocol B[d]	
37	H	H	EtO	2		2000
40	H	H	Me_2N	2	0.1	320
41	H	H	Et_2N	3	0.2	130
42	H	H		3	0.1	95
38	Me	H	EtO	4	0.5	610
43	Me	H	Et_2N	2	0.2	130
39	Me	Me	EtO	3	0.3	150
44	Me	Me	Me_2N	3	0.1	160
45	Me	Me	Et_2N	2	0.2	42
46	Me	Me	$n\text{-}Pr_2N$	5	0.4	70
47	Me	Me			0.12	81
48	Me	Me		2	0.2	40
49	Me	Me		3	0.2	65

[a]Inhibition of binding of [^{125}I]-buserelin to rat pituitary GnRH receptor.
[b]Inhibition of GnRH-stimulated LH release from rat pituitary cells.
[c]Absence of BSA.
[d]Presence of 0.1% BSA.

Thus, we have found that ester, and especially carboxamide, groups at the indole 5-position of tryptamine-derived GnRH antagonists confer potent activity in binding and functional assays. This was demonstrated for compounds bearing a phenol or methanesulfonamide end group on the *N*-(4-phenylbutyl) side chain. In each case, amides derived from medium-sized secondary amines were preferred, especially for inhibition of LH release from rat pituitary cells. With the amide carbonyl directly attached to the indole 5-position, branched substituents such as *N,N*-diisobutylcarboxamide were favored. When a branched (*gem*-dimethylated) spacer was inserted between the indole and the carbonyl, good functional activity was achieved even with simple tertiary amides derived from diethylamine or pyrrolidine.

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