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2-Arylindoles as Gonadotropin Releasing Hormone (GnRH) Antagonists: Optimization of the Tryptamine Side Chain

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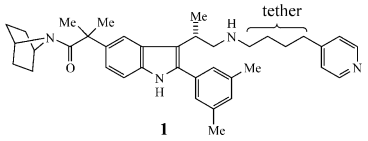
Abstract—A series of 2-arylindoles containing novel heteroaromatic substituents on the tryptamine tether, based on compound **1**, was prepared and evaluated for their ability to act as gonadotropin releasing hormone (GnRH) antagonists. Successful modifications of **1** included chain length variation (reduction) and replacement of the pyridine with heteroaromatic groups. These alterations culminated in the discovery of compound **27kk** which had excellent in vitro potency and oral efficacy in rodents. © 2002 Elsevier Science Ltd. All rights reserved.

Previous communications from these laboratories described 3-arylquinolones[1] and 2-arylindoles[2] as potent non-peptidyl GnRH antagonists (Fig. 1). Notable discoveries within the 2-arylindole class included the potency enhancing 3,5-dimethylphenyl[2a] and the C(5)-dimethylacetamide substituents,[2d,e] introduction of a pyridine side chain terminus as a replacement for the earlier metabolically labile phenol group,[2f] and incorporation of the (*S*)-β-methyl group which improved the selectivity profile.[2g] Indole **1** was characterized by excellent in vitro potency in both our binding (hGnRH) and functional assays (hPI)[3] and had good oral bioavailability in dogs.

Despite these favorable characteristics, the in vivo duration of action for indole **1** was low. We attributed this in part to low systemic drug levels and fast clearance. At this juncture, we were confident that the 2-aryl and 5-acetamide positions were optimized for potency and pharmacokinetics. To improve this lead, we studied the structure–activity relationships of the tryptamine tether and end terminus. In this letter, we will present a series of heteroaromatic replacements for the pyridine moiety of GnRH antagonist **1**.

The tryptamine core of **1** (**25**, Scheme 1) was assembled by either Fischer[4] or Larock[5] methods as previously described. Attachment of the heteroaromatic side chain was accomplished by either reductive amination of aldehydes **23** with tryptamines **25**, or by the Fukuyama[6] amine synthesis which required alcohols **24** and sulfonamides **26**. The requisite aldehydes and alcohols were prepared by standard methods that will be outlined below. Installation of the side chains found in compounds **23** and **24** was envisioned to be derived from a halogenated precursor such as **22**.

A number of heterocyclic syntheses are outlined in Schemes 2–6. 6-Bromoisoquinoline **4** was prepared from



hGnRH = 0.7 nM
hPI = 5.7 nM
Clp = 26.5 mL/min/kg (dog)
$t_{1/2}$ = 9.5 hr (dog)
%F = 23% (dog); %F = 11% (rat)

Figure 1. Biological properties of potent GnRH antagonist **1**.

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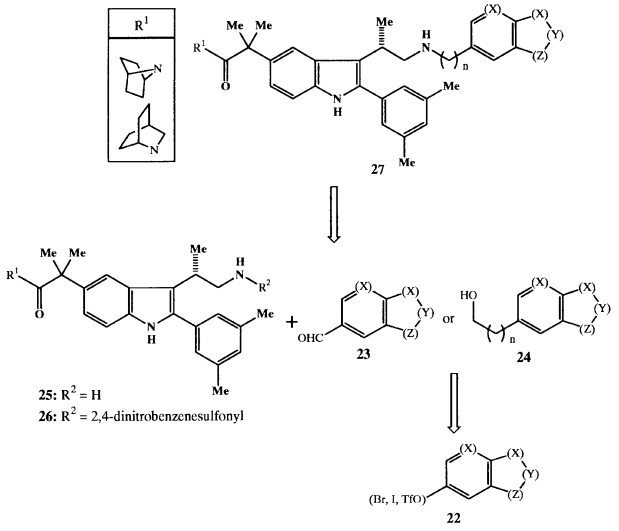
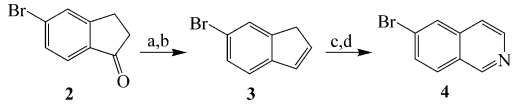
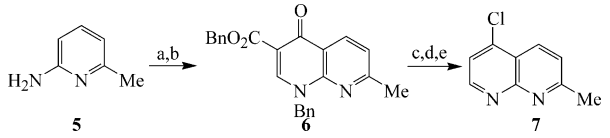


Scheme 1. Retrosynthetic preparation of indole analogues.



Scheme 2. Reagents and conditions: (a) $NaBH_4$, MeOH (100%); (b) H_2SO_4, C_6H_6, 80 °C (92%); (c) (i) O_3, CH_2Cl_2–MeOH, −78 °C; (ii) Me_2S; (d) NH_4OH (37%).

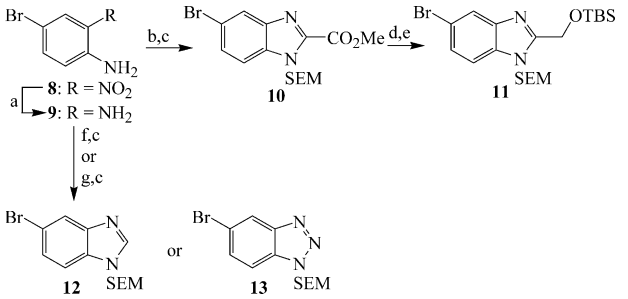


Scheme 3. Reagents and conditions: (a) (i) ethoxymethylene malonate, xylenes, 135 °C (91%); (ii) Ph_2O, 230 °C (48%); (b) KOH, EtOH; K_2CO_3, BnBr, DMF; (c) (i) NaOH, EtOH; (ii) KCN, DMSO, 100 °C (78%); (d) H_4NO_2CH, $Pd(OH)_2$, MeOH (76%); (e) $POCl_3$, toluene, 100 °C (76%).

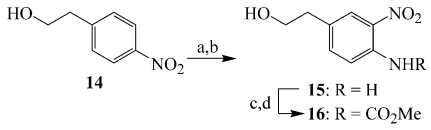
5-bromoindanone **2** by ketone reduction and subsequent acid catalyzed elimination of the alcohol to indene **3** (Scheme 2). Ozonolysis of indene **3** and subsequent treatment with ammonium hydroxide gave isoquinoline **4**.[7]

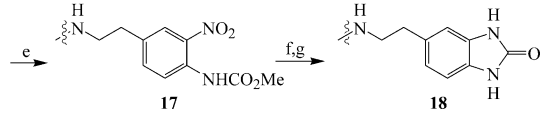
Condensation of 2-amino-6-methylpyridine **5** and ethoxymethylene malonate followed by thermal cyclization, ester hydrolysis, and double benzylation afforded the vinylogous-amide **6** (Scheme 3).[8] The C(6)-methyl group proved critical for the Friedel–Crafts cyclization. Omission of this substituent resulted in intramolecular acylation on the pyridine nitrogen. Removal of the ester was accomplished in two steps by first, hydrolysis of the ester followed by decarboxylation of the acid with KCN in hot DMSO.[9] Napthyridine **7** was completed by hydrogenation of the *N*-benzyl substituent and chlorination ($POCl_3$).

Benzimidazoles **10**, **11** and **12** along with benzotriazole **13** were prepared from diamine **9**, which was available from hydrazine reduction of **8** (Scheme 4). Treatment of

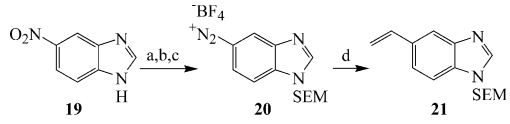


Scheme 4. Reagents and conditions: (a) $Cl_3Fe{\cdot}6H_2O$, H_2NNH_2, MeOH (97%); (b) (i) $MeOC(NH)CCl_3$, 5% AcOH (aqueous) (62%); (ii) MeOH, 67 °C (90%); (c) NaH, DMF; SEMCl (77%); (d) (i) DIBAL-H, CH_2Cl_2, −78 °C (74%); (ii) $NaBH_4$, MeOH (100%); (e) TBSCl, imidazole, DMF (98%); (f) $HC(OEt)_3$, 125 °C (79%); (g) $NaNO_2$, 5% AcOH (75%).





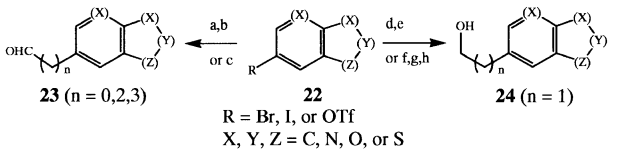
Scheme 5. Reagents and conditions: (a) (i) Ac_2O, DMAP, pyridine, CH_2Cl_2 (97%); (ii) H_4NO_2CH, 10% Pd/C, MeOH, 60 °C (78%); (b) (i) KNO_3, TFAA (89%); (ii) K_2CO_3, MeOH; (c) $ClCO_2Me$, 1,2-DCE, pyridine (60%); (d) K_2CO_3, MeOH (88%); (e) (i) Ph_3P, DEAD, **26**, benzene; (ii) *n*-$PrNH_2$, CH_2Cl_2 (64% two steps); (f) H_4NO_2CH, 10% Pd/C, MeOH, 60 °C (100%); (g) AcOH, 110 °C (60%).



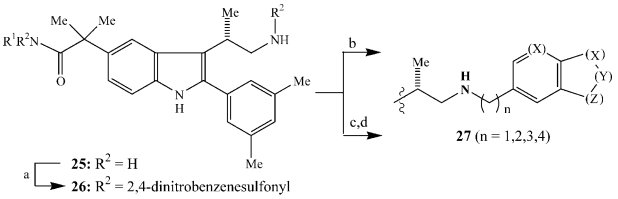
Scheme 6. Reagents and conditions: (a) NaH, DMF; SEMCl (60%); (b) $Cl_3Fe{\cdot}6H_2O$, H_2NNH_2, MeOH (97%); (c) $NaNO_2$, HBF_4, H_2O; (d) tributyl(vinyl)tin, $Pd_2(dba)_3$, MeCN (40%).

9 with methyl 2,2,2-trichloroacetimidate[10a] followed by methanolysis[11] and *N*-SEM protection[12] gave **10**. Reduction of **10** followed by TBS protection of the alcohol provided **11**. Alternatively, exposure of **9** to triethyl-orthoformate[10b] and subsequent protection furnished **12**. Benzotriazole **13** was readily prepared by treatment of **9** with sodium nitrite[13] in acetic acid and subsequent protection of the heterocyclic nitrogen.

For benzimidazalinone **18**, we found it expedient to begin with the tether pre-installed. After acetylation of **14** and nitro group reduction, nitration (potassium nitrate and trifluoroacetic anhydride) occurred *ortho* to the aniline concomitant with trifluoroacetamide protection of the aniline (Scheme 5). Unfortunately, selective hydrolysis proved to be capricious. Thus, treatment under basic methanol conditions provided amino-alcohol **15**. Global protection of **15** using methyl chloroformate and selective hydrolysis of the carbonate gave intermediate **16**. Using the protocol of Fukuyama, **16** and **26** were subjected to Mitsunobu conditions and subsequent desulfonylation under basic conditions



Scheme 7. Reagents and conditions: (a) 2-propenal 1,1-diethyl acetal (or 3-butenal 1,1-diethyl acetal), 9-BBN, THF; $Cl_2Pd(dppf)$, K_3PO_4, 70 °C; (b) TFA, H_2O; (c) $Cl_2Pd(Ph_3P)_2$, NaO_2CH, DMF, 95 °C ($n=0$); (d) tributyl(vinyl)tin, $Cl_2Pd(Ph_3P)_2$, DMF, 95 °C; (e) 9-BBN, THF; H_2O_2, NaOH; (f) NBS, DMSO-H_2O; (g) *t*-BuOK, THF-*t*-BuOH; (h) 10% Pd/C, H_4NO_2CH, MeOH, 65 °C.



Scheme 8. Reagents and conditions: (a) 2,4-dinitrobenzenesulfonyl chloride, $NaHCO_3$, H_2O–CH_2Cl_22; (b) **23**, **25**, $NaCNBH_3$, HOAc-THF-MeOH; (c) **24**, **26**, Ph_3P, DEAD, benzene; (d) *n*-$PrNH_2$, CH_2Cl_2.

furnished **17**. After reduction of the nitro group, the *o*-aminocarbamate was refluxed in acetic acid[14] which afforded benzimidazalinone **18**.

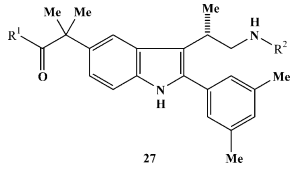
Diazonium salt **20** was utilized the as the nucleophillic component in the Stille coupling reaction (Scheme 6). Protection of heterocycle **19** with SEM-Cl was followed by nitro group reduction and oxidation which afforded diazo compound **20**. The ensuing Stille reaction with tributyl(vinyl)tin was very sensitive to the counter ion. In fact, the tetrafluoroborate ion was required for the successful coupling. In contrast to couplings with aryl bromides or triflates, diazonium intermediate **20** participated in the Stille reaction at temperatures as low as −20 °C.[15]

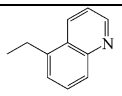
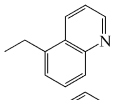
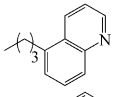
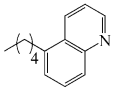
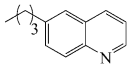
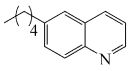
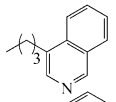
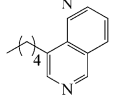
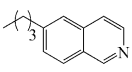
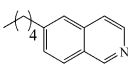
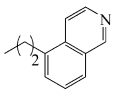
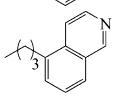
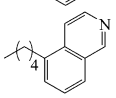
Specifically for the 3- and 4-atom tethers ($n=3$ and 4, respectively), the appropriate alkenal 1,1-diethyl acetal was transformed to the trialkyl borane and reacted with the heteroaromatic intermediates **22** under the Suzuki coupling protocol (Scheme 7).[16] Subsequent hydrolysis of the acetal with aqueous TFA liberated aldehydes **23**. The benzaldehydes ($n=0$) were in turn prepared by a palladium catalyzed formylation.[17] Aldehydes **23** were then coupled to amines **25** under reductive-amination conditions (Scheme 8).

Since phenylacetaldehydes failed to couple cleanly under reductive amination protocols, we opted for Fukuyama's method for amine synthesis which required alcohols **24**. Stille[18] coupling of intermediates **22** with tributyl(vinyl)tin furnished the styrene derivatives which were transformed to alcohols **24** via hydroboration–oxidation sequence for many substrates. In some cases however, certain heterocycles were susceptible to reduction with 9-BBN. In those instances, the styrene was converted to the bromohydrin (NBS-H_2O),[19] base induced closure to the epoxide (*t*-BuOK),[20] followed by benzylic reduction to give the desired alcohol (10% Pd/C, H_4NO_2CH).[21] Finally, alcohols **24** were combined with sulfonamides **26** under Mitsunobu conditions followed by base catalyzed desulfonylation which provided indoles **27** (Scheme 8).

As a continuation of the pyridylbutyl end group SAR, we have recently prepared a series of fused pyridine mimetics (i.e., quinolines and isoquinolines) with varied tether lengths in order to improve the in vivo properties

Table 1. SAR of **27** with quinoline and isoquinoline end-groups



27	R^1	R^2	hGnRH IC_{50} (nM)[a]	hPI IC_{50} (nM)[b]
a			27.5	420
b			15.3	315
c			2.4	131
d			1.9	46.4
e			3.0	17.8
f			1.1	11.5
g			2.1	7.5
h			2.1	10.2
i			0.7	4.6
j			3.6	5.8
k			0.6	34.7
l			0.9	5.0
m			1.5	6.8

[a]Inhibition of [^{125}I]buserelin binding to human pituitary GnRH receptor.
[b]Inhibition of GnRH-stimulated [^{3}H]inositol phosphate hydrolysis.

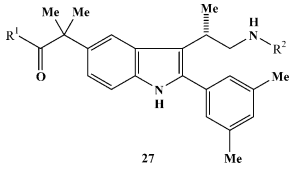
and off-target activities of the indole lead **1** (Table 1). In our initial series, 5-alkylquinolines **27a**, **27c**, and **27d** were synthesized without the chiral methyl substituent. Comparison of **27a** and **27b** revealed that the (*S*)-β-methyl group afforded a two fold improvement in binding affinity to the GnRH receptor. In addition, this group also imparted greater selectivity versus off target activities. Compounds **27c** and **27d** were noticeably more potent than **27a**, indicating a preference for the longer tether designs (3 or 4 atoms). The remaining quinolines and isoquinolines (**27e**–**m**) in Table 1 displayed similar in vitro activities to one another (hPI $IC_{50's} = 5$–35 nM). Compound **27k**, the only two-atom tether analogue in Table 1, demonstrated the best binding affinity to the GnRH receptor but the functional activity was less than predicted.

To distinguish the two-atom and four-atom tether designs, we obtained pharmacokinetic data (dog) on compounds **27k** and **27m**. The shorter tether revealed several advantages during this in vivo comparison. For example, the terminal plasma half-life of **27k** was doubled (1.9 vs 1.0 h), the plasma clearance rate was nearly 10 times less (5.8 vs 49.2 mL/min/kg) and the oral bioavailability was over 2-fold higher than **27m** (10 vs 4%). These findings were consistent with other studies in our group and was later found to be consistent across heteroaromatic termini.

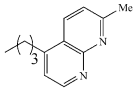
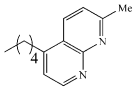
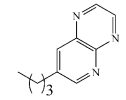
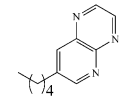
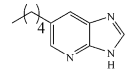
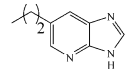
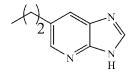
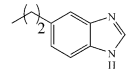
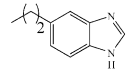
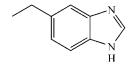
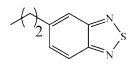
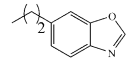
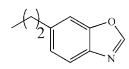
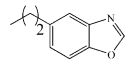
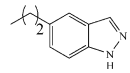
Encouraged by the initial results from the quinoline class, we surveyed a variety of more sophisticated heterocycles. Napthyridines **27n**–**o**, pyrazinylpyridines **27p**–**q** along with imidazopyridine **27r** displayed very promising in vitro results, although no improvement in potency over the quinolines and isoquinolines was observed (Table 2). A modest preference for the four-atom tether was observed in this series. Interestingly, imidazopyridine **27s**, attached through a two-carbon tether, demonstrated functional antagonism equal to **27r**. This was in contrast to that observed in the isoquinoline series (cf. **27k** and **27m**). The closely related benzimidazole analogue **27u** was equipotent to **27s**. Additionally, the isoquinuclidine amides (**27t** and **27v**) were indistinguishable in terms of in vitro potency from the azanorbornane amides (**27s** and **27u**).[21] Heteroatom variations of the five-membered ring, including benzothiadiazole **27x**, benzoxazoles **27y**, **27z** and **27aa** and indazole **27bb**, provided additional examples of functionally potent GnRH antagonists.

Based on the attractive properties of **27s**–**v**, we obtained pharmacokinetic data (dog) on these analogues. In general, the benzimidazoles were cleared from plasma more slowly and had longer terminal half-lives as compared to the imidazopyridines. This data in part accounts for the large discrepancy in oral bioavailability between **27v** and **27t** (63% vs 16%, respectively). During these studies, however, we discovered that **27t** and **27v** were potent inhibitors of the cytochrome P450 3A4 enzyme with $IC_{50's}$ of 4 μM and 100 nM, respectively.[22] In fact, Cyp3A4 was a common liability in this class of analogues; for example, **27k**, **27x** and **27y** were found to have activities between ($IC_{50} = 1$–2 μM).

Table 2. SAR of **27** with novel heteroaromatic end-groups

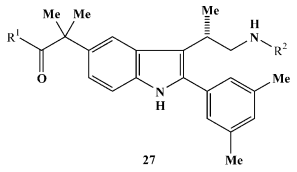


27

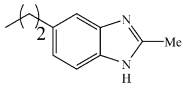
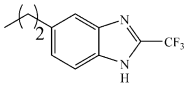
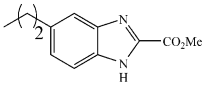
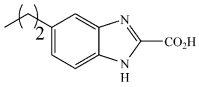
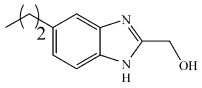
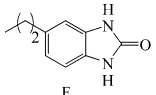
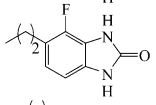
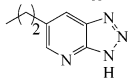
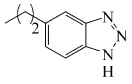
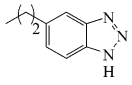
27	R^1	R^2	hGnRH IC_{50} (nM)[a]	hPI IC_{50} (nM)[b]
n			1.1	16.2
o			0.6	8.4
p			0.8	10.9
q			0.4	7.9
r			0.4	4.6
s			0.4	2.5
t			0.3	4.5
u			0.4	2.6
v			0.3	4.5
w			16.5	43.9
x			0.5	11.4
y			0.4	2.0
z			0.6	3.9
aa			0.3	9.0
bb			1.1	1.5

[a]Inhibition of [^{125}I]buserelin binding to human pituitary GnRH receptor.
[b]Inhibition of GnRH-stimulated [^{3}H]inositol phosphate hydrolysis.

Table 3. SAR of **27** with novel heteroaromatic end-groups



27

27	R^1	R^2	hGnRH IC_{50} (nM)[a]	hPI IC_{50} (nM)[b]
cc			0.4	13
dd			0.9	101
ee			0.3	7.6
ff			0.4	6.5
gg			0.7	5.0
hh			0.6	2.0
ii			0.7	27.9
jj			0.6	2.8
kk			0.3	2.5
ll			0.6	2.0

[a]Inhibition of [^{125}I]buserelin binding to human pituitary GnRH receptor.
[b]Inhibition of GnRH-stimulated [^{3}H]inositol phosphate hydrolysis.

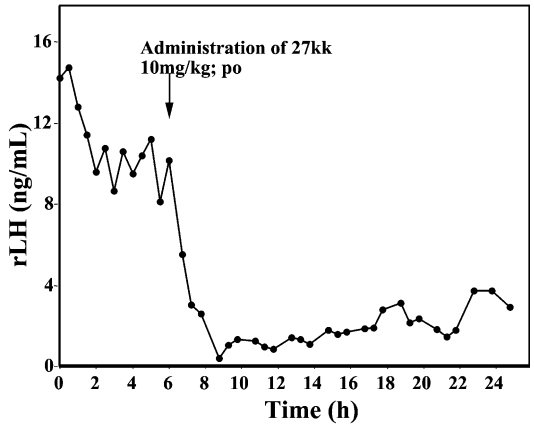


Figure 2. Effect of oral **27kk** (administration at time = 6 h indicated by arrow) on LH release in a castrated male rat, as described in ref 2i. The data shown are for a single male rat ($n = 1$).

Based on the superior pharmacokinetic profile of the benzimidazole class, we formulated a strategy to attenuate the P_{450} inhibitory properties while maintaining GnRH potency in this series. Incorporation of a C(2)-alkyl substituent on the benzimidazole (**27cc** and **27dd**) successfully diminished the P450 inhibition (5 and >10 μM, respectively, vs 100 nM), yet with concomitant reduction of functional GnRH potency (Table 3). The functional potency was restored with ester (**27ee**), acid (**27ff**) and hydroxymethyl (**27gg**) substitution. Acid **27ff** had a low plasma clearance rate in dog (24.6 mL/min/kg) compared to all other acids tested, but had no oral bioavailability.

The potency of benzimidazoles **27ee–gg** reinforced the notion that basic substituents were not required for functional antagonism (cf., phenols and sulfonamides)[2c] and that polar groups capable of participating in hydrogen bonding interactions were well tolerated. Benzimidazolinone **27 hh** was a promising compound in terms of GnRH potency (PI: $IC_{50} = 2.0$ nM) but suffered from low oral bioavailability (5%) in dogs. Fluorine incorporation onto the benzimidazolinone (**27ii**) had a negative impact on GnRH functional activity. Finally, benzotriazole derivatives **27jj**, **27kk**, and **27ll** demonstrated an acceptable balance between functional activity and P_{450} inhibition ($IC_{50} = 7.5$ μM for **27kk**). Moreover, **27kk** and **27ll** had moderate oral bioavailability (20 and 37% in dogs, respectively) with low plasma clearance (5.0 and 9.7 mL/min/kg, respectively) and reasonable terminal half-lives (7.2 and 2.7 h, respectively).

Benzotriazole **27kk** proved to be efficacious in the castrated rat assay which measures the ability of a GnRH antagonist to reduce the circulating levels of LH. In an intact rat, the levels of LH are pulsatile and varied, whereas in a castrated rat the levels are more consistent and elevated. The first six h of the experiment served to establish the basal level of circulating LH for the specific rat (Fig. 2). Compound **27kk** effectively inhibited LH release over a range of oral doses (1, 5, 10, and 20 mpk). In a representative experiment, a single oral dose at 10 mpk substantially reduced plasma LH levels for approximately 14 h.

In conclusion, we have demonstrated that the pyridine ring can be replaced with a variety of heteroaromatic rings while maintaining GnRH potency. In addition, a basic substituent on the tryptamine tether was not critical for GnRH antagonist activity as had been previously shown with the phenol and sulfonamide analogues. In this study, benzotriazole **27kk** was a potent, orally active GnRH antagonist that substantially decreased the cytochrome P450 3A4 inhibitory activity over the closely related pyridine and benzimidazole series.

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References and Notes

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3. See ref 1c for details concerning the in vitro assays. The $IC_{50's}$ reported herein are minimally an average of two titrations.

4. For synthesis of the tryptamine core via a Fischer-indole method, see ref 2g.

5. For application of the Larock method, see: Walsh, T. F.; Toupence, R. B.; Ujjainwalla, F.; Young, J. R.; Goulet, M. T. *Tetrahedron* **2001**, *57*, 5233.

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22. The effect of selected compounds on cytochrome P450 3A-catalyzed erythromycin *N*-demethylation, testosterone 6β-hydroxylation and midazolam 1′-hydroxylation was studied after co-incubation at different concentrations (0.05–10 μM), with an appropriate range of substrate concentrations: erythromycin at 50–500 μM, testosterone at 20–1000 μM and midazolam at 1–50 μM. The human liver microsomes in these studies were mixtures of preparations from 5–10 subjects. The incubations were carried out at 37 °C under linear conditions for substrate turnover with respect to microsomal protein concentration and incubation time. The microsomal protein concentration used was 0.25 mg/mL for the midazolam hydroxylation, 0.5 mg/mL for the testosterone and 2 mg/mL for the erythromycin assay. The possibility of time-dependent inhibition was investigated by pre-incubating compounds (0.1–50 μM) with human liver microsomes in the presence of an NADPH-regenerating system for 0–30 min prior to the addition of 250 μM testosterone. Extracts of the incubation mixtures were analyzed by HPLC with UV detection (testosterone 6β-hydroxylation, midazolam 1′-hydroxylation) or LC–MS/MS (midazolam 1′-hydroxylation and erythromycin *N*-demethylation). The values for the apparent K_m and V_{max} were estimated by fitting the data to the Michaelis–Menten equation, using non-linear regression.