

Benzimidazole derivatives as novel nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonists. Part 2: Benzimidazole-5-sulfonamides

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Abstract—The 2-cyclopropyl substituted benzimidazole **2** has been used as a starting point for further optimization of an LHRH antagonist series. SAR studies revealed that a *tert*-butyl urea fragment connected through a simple carbon chain would improve activity. Further modification of the benzylsulfonamide moiety led to the discovery of **23** (IC₅₀: 4.2 nM).

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1. Introduction

Nonpeptidic luteinizing hormone-releasing hormone (LHRH) antagonists are interesting novel therapeutics for hormone dependent disease states such as endometriosis, prostate cancer and benign prostate hyperplasia.¹ We previously reported the discovery of a new class of benzimidazoles as functional LHRH antagonists with submicromolar potency on both human and rat receptors (**1**, IC₅₀ = 0.12 μM).²

In this study, we would wish to report a related series of compounds, exemplified by **2**, that allowed for the discovery of single digit nanomolar LHRH antagonists (Fig. 1).

2. Chemistry

The central intermediate **3**² (Scheme 1) was coupled to Boc-protected 3-amino propionic acid yielding the

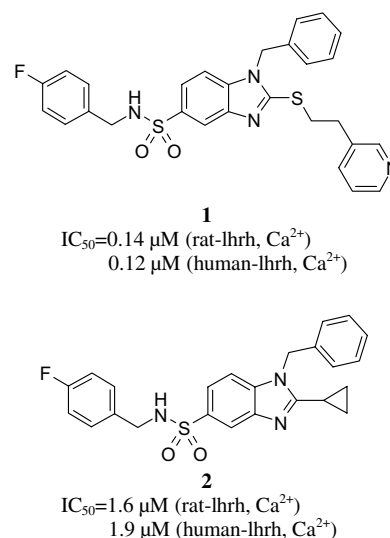
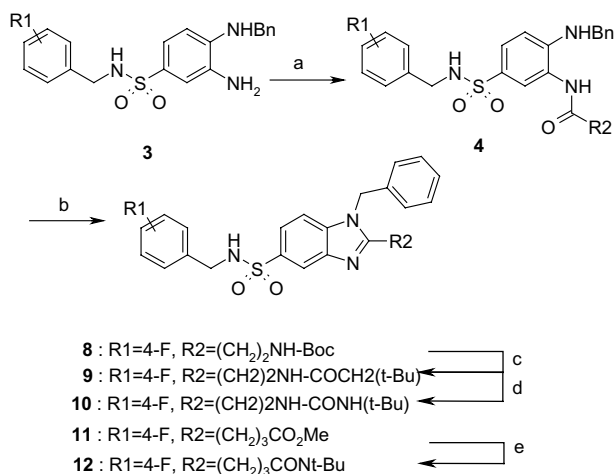


Figure 1. Functional activity of C-linked compound **2**.

corresponding amide **4**, which was subjected to acid-induced cyclization to furnish the benzimidazoles **5–8**. After deprotection, **8** was converted to *tert*-butylurea **10** (R1 = 4-F) using *tert*-butyl isocyanate.³ Similarly, the alkyl or aryl urea derivatives **13–25** were obtained. Compound **8** was coupled with 3,3-dimethyl butyric

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Scheme 1. Reagents and conditions: (a) RCO₂H, WSCI, HOBT, triethylamine, THF, rt, 90%; (b) compound **8**, HOAc, 90°C, 70%, compound **11**, HOAc, 90°C, 41%; (c) 4N HCl, dioxane, rt, 99%, then, *tert*-butylacetyl chloride, triethylamine, CH₂Cl₂, rt, 38%; (d) 4N HCl, dioxane, rt, 99%, then isocyanic acid *tert*-butylester, triethylamine, CH₂Cl₂, rt, 56%; (e) 1N LiOH, THF, rt, 37%, then, *tert*-butylamine, WSCI, HOBT, triethylamine, THF, rt, 71%.

acid furnishing **9**. Diaminosulfonamide **3** was coupled and cyclized with glutaric acid monomethyl ester to give benzimidazole **11**. Hydrolysis and renewed amide formation furnished compound **12**.

3. Results and discussion

All synthesized compounds were evaluated as functional antagonists on cells transfected with rat and human receptors, respectively (Tables 1 and 2).² All IC₅₀ values indicate the mean of two experiments each run in triplicate. The geometry of the propyl substituent appeared to directly influence the biological activity of **2**. Whereas the *n*-propyl compound **5** was inactive, the isopropyl derivative showed a 5-fold improvement in potency (**6**). Interestingly, despite the inactivity of **5** and the primary amine **7**, the Boc-protected amine **8** retained activity, prompting us to investigate the SAR of the carbamate even further. Whereas the *tert*-butyl acetamide **9** showed similar potency, the isomeric pivaloate **12** was less potent. The corresponding *tert*-butyl urea **10** was the first example of a double-digit nanomolar compound. Taken together, the SAR observed among **8–10** and **12** clearly indicates the importance of two hydrogen-bond donors for optimal interaction with the LHRH receptor. Similar ureas with bulky substituents have been described by other groups.⁴ Substituting the *tert*-butyl group with other alkyl substituents such as isopropyl (**13**), ethyl (**14**) or neopentyl (**15**) reduced activity. Similarly, chain prolongation (**16**) diminished potency, suggesting the importance of the correct spatial orientation of the bulky aliphatic group. Interestingly however, this group can be replaced by a phenyl substituent, and the *ortho*-substituted derivatives **17/18** represent two further examples of double digit nanomolar LHRH antagonists.

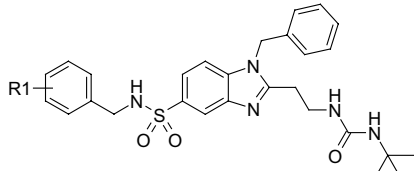
Table 1. Functional activity of compounds **5–10** and **12–18**



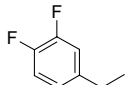
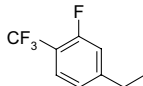
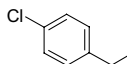
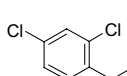
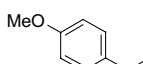
Cmpd	X	R	IC ₅₀ (μM)	
			r-lhrh	h-lhrh
5	CH ₂	–CH ₂ CH ₃	>10	>10
6	CHMe	–CH ₃	0.69	0.39
7	CH ₂	–CH ₂ NH ₂	>10	>10
8	CH ₂		0.54	0.74
9	CH ₂		0.84	2.6
10	CH ₂		0.012	0.020
12	CH ₂		0.23	0.40
13	CH ₂		0.079	0.15
14	CH ₂		0.38	0.69
15	CH ₂		0.030	0.11
16	CH ₂		0.083	0.18
17	CH ₂		0.053	0.066
18	CH ₂		0.050	0.083

This discovery prompted us to re-investigate the SAR of the sulfonamide side chain within the *tert*-butyl urea class (Table 2). Similar to the SAR described in our previous communication, electron-withdrawing substituents in *para*-position were preferred. *ortho*-(**20**, **24**), *meta*-(**21**, **22**) or electron donating substituents (**25**) clearly reduced potency. In contrast to trends observed in our earlier series however, merely exchanging **10**'s F-atom by a chloro substituent led to **23**, which was the first single-digit nanomolar LHRH inhibitor within the series, improving potency of our initial lead by three orders of magnitude.

In summary, we have identified a novel series of nonpeptide LHRH antagonists that could be optimized towards

Table 2. Functional activity of compounds 19–25



Cmpd	R1-ArCH ₂	IC ₅₀ (μM)	
		r-lhrh	h-lhrh
19		0.31	0.49
20		0.45	0.75
21		0.11	0.17
22		0.051	0.057
23		0.0039	0.0042
24		0.014	0.022
25		0.20	0.34

the single-digit nanomolar range. The compounds exhibit a *tert*-butyl urea fragment as a prerequisite, indispensable for high potency.

References and notes

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- Fonseca, T.; Gigante, B.; Gilchrist, T. L. *Tetrahedron* **2001**, 57, 1793. Typical procedure to prepare 2-[2-(3-*tert*-butylureido)-ethyl]-1*H*-benzimidazole-5-sulfonamide derivatives (synthesis of compound **10**): A solution of {2-[2-benzylamino-5-(4-fluoro-benzylsulfamoyl)-phenylcarbamoyl]-ethyl}-*tert*-butylcarbamate **4** (505mg, 0.910mmol) in 10mL of acetic acid was heated at 90°C for 3h. After cooling to room temperature, the mixture was concentrated in vacuo, to give crude compound **8**. The crude mixture was diluted in 10mL of CH₂Cl₂ and treated with 4N HCl/1,4-dioxane to give a white precipitate as the deprotected benzimidazole HCl salt. After filtering, and drying under reduced pressure, the HCl salt (100mg, 0.210mmol) was suspended in 1.5mL of CH₂Cl₂. To the suspension was added triethylamine (0.0590mL) and *tert*-butyl isocyanate (62.6mg, 0.630mmol) and the mixture was stirred at room temperature for 2h. The mixture was diluted with CH₂Cl₂ and the organic layer was washed with water and brine. After removing the solvent, the residue was triturated with ether to give the desired 1-benzyl-2-[2-(3-*tert*-butylureido)-ethyl]-1*H*-benzimidazole-5-(4-fluorobenzyl)sulfonamide **10** (70.7mg, 63% yield for two steps) as a white precipitate. ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.19 (9H, s), 2.95–2.98 (2H, t, *J* = 6.6Hz), 3.44–3.47 (2H, t, *J* = 6.9Hz), 3.93–3.94 (1H, d, *J* = 6.0Hz), 5.56 (2H, s), 5.79 (1H, s), 5.83–5.85 (1H, t, *J* = 6.0Hz), 7.04–7.07 (2H, t, *J* = 9.14Hz), 7.11–7.13 (2H, d, *J* = 6.9Hz), 7.24–7.35 (5H, m), 7.61–7.67 (2H, dd, *J* = 8.5Hz, 21Hz), 8.03–8.05 (2H, m).
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