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Bioorganic & Medicinal Chemistry Letters 15 (2005) 2265–2269
Bioorganic & Medicinal Chemistry Letters

Benzimidazoles as non-peptide luteinizing hormone-releasing hormone (LHRH) antagonists. Part 3: Discovery of 1-(1*H*-benzimidazol-5-yl)-3-*tert*-butylurea derivatives

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Received 1 February 2005; accepted 3 March 2005

Abstract—1-(1*H*-Benzimidazol-5-yl)-3-*tert*-butylurea derivatives have been identified as a novel class of non-peptide luteinizing hormone-releasing hormone (LHRH) antagonists. Herein, we disclose the synthesis and structure–activity relationships (SAR) of this class resulting in the identification of compound **12c**, with dual functional activity on human and rat receptors (rat LHRH: IC_{50} = 120 nM; human LHRH: IC_{50} = 18 nM). These SAR studies suggest that 1-(1*H*-benzimidazol-5-yl)-3-*tert*-butylurea is a new pharmacophore for small molecule LHRH antagonists.

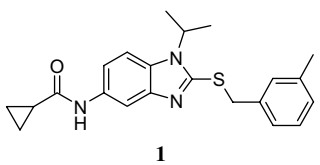
1. Introduction

Luteinizing hormone-releasing hormone (LHRH) antagonists have been investigated by many groups as a potential new treatment for hormone-dependent diseases, such as endometriosis, breast cancer, and prostate cancer.[1,2] Clinical use of peptidic LHRH agonists is hampered by desensitization of the receptor resulting in suppression of serum testosterone to castration levels. This treatment is accompanied with undesirable side effects such as the concomitant 'flare' effect. Clinical evidence suggests that peptidic LHRH antagonists directly lower steroid hormone levels and alleviate disease symptoms without 'flare' effects.[2,3] In addition, small molecule non-peptidic LHRH antagonists would possess advantages over existing peptidyl therapeutics due to their potential for oral administration.

In previous publications, our group described benzimidazoles as LHRH antagonists.[4] In order to reduce attrition at later stages of development, additional efforts have been devoted toward searching for new pharmacophores of small molecule LHRH antagonists. Starting with compound **1**, which was identified by high throughput screening of our compound library, a series of benzimidazoles was synthesized and evaluated as LHRH antagonists (Fig. 1). In this report, we describe the synthesis and SAR of benzimidazoles. Whereas the molecular core is identical to those in the earlier series, the substitution pattern demonstrates unprecedented SAR, probably suggesting an alternative binding mode.

2. Chemistry

The synthesis of various benzimidazoles is outlined in Scheme 1.[5] Common intermediate anilines **5** were prepared from **2** by standard substitution and reduction methods. Anilines **5** were treated with carbon disulfide



1
IC_{50}= > 10 μM (rat-LHRH, Ca^{2+})
6.5 μM (human-LHRH, Ca^{2+})

Figure 1. Biological activity of lead compound **1**.

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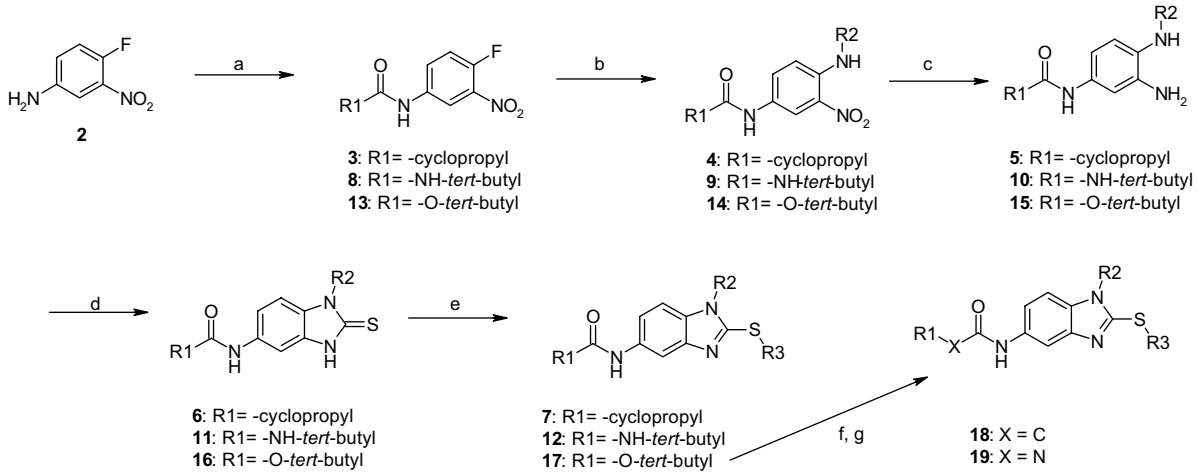
doi:10.1016/j.bmcl.2005.03.030



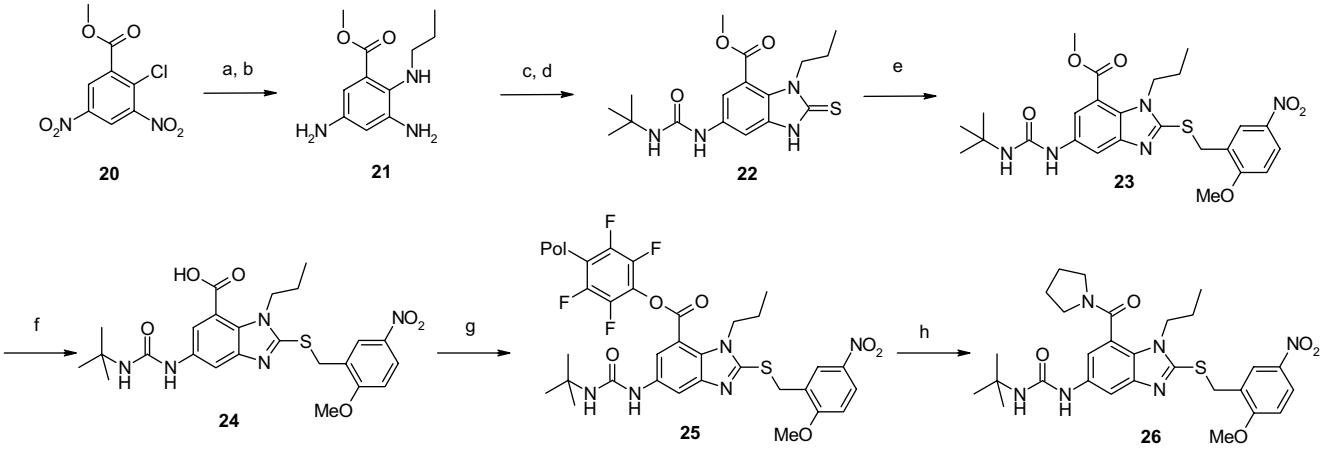
Scheme 1. Reagents and conditions: (a) cyclopropanecarbonyl chloride, Et_3N, CH_2Cl_2, rt, or 2-isocyanato-2-methylpropane, Et_3N, CH_2Cl_2, rt, or di-*tert*-butyl carbonate, Et_3N, CH_3CN, rt; (b) $R2NH_2$, Et_3N, CH_3CN, 50 °C; (c) $SnCl_2$–$2H_2O$, EtOH, DMF, 50 °C; (d) CS_2, DIPEA, EtOH, 60 °C; (e) R3Br, DIPEA, THF, rt, or R3OH, DEAD, Ph_3P, THF, rt; (f) 4 N HCl–dioxane, rt; (g) $R1CH_2COOH$, Et_3N, CH_2Cl_2, rt, or R1NCO, Et_3N, CH_2Cl_2, rt.

to give thioureas **6**, which were treated with benzyl bromide under basic condition or subjected to a Mitsunobu reaction with various alcohols to afford **7**. A similar synthetic strategy was applied for the synthesis of **12** and **17**. Compound **2** was reacted with 2-isocyanato-2-methylpropane or di-*tert*-butyl carbonate instead of acyl chloride. After four steps, **12** and **17** were obtained. Deprotection of **17** was achieved under acidic condition to give the amine as its HCl salt. These were converted to amides **18** or urea **19** under standard conditions. Compounds in Table 4 were prepared from a common intermediate **23**, which was synthesized via **20**. The synthesis of compound **26** is outlined in Scheme 2. Aniline **21** was prepared from **20** by standard methods using substitution and reduction reactions.[5] Compound **21** was treated with carbon disulfide to prepare the corresponding thiourea, which was converted to **22**. Compound **22** was treated with 2-methoxy-5-nitrobenzyl bromide under basic condition to give **23**, which gave carboxylic acid **24** after hydrolysis. Compound **24** was immobilized on solid support to give a TFP polymer-bound ester **25**, which was treated with pyrrolidine to furnish crude **26**.[6] Excess amine and carboxylic acid were removed with methylisocyanate polystyrene (PS-NCO) and 1,5,7-triazabicyclo[4,4,0]dec-5-ene polystyrene (PS-TBD), respectively, to give pure material **26**.[7] Compounds **26a**–**m** were synthesized similarly.

3. Results and discussion

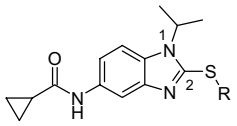
The synthesized compounds were evaluated as functional antagonists of both rat and human receptors according to methods in the literature (Tables 1–4).[4]

First, substitution at the 2-position of the benzimidazole core was explored (Table 1). The substitution pattern of the phenyl ring had a strong effect on potency with



Scheme 2. Reagents and conditions: (a) *n*-propylamine, CH_2Cl_2, rt, 89%; (b) Pd/C, H_2, AcOEt, rt, quant.; (c) CS_2, DIPEA, EtOH, 60 °C, quant.; (d) 2-isocyanato-2-methylpropane, Et_3N, THF, 40 °C, 98%; (e) 2-(bromomethyl)-1-methoxy-4-nitrobenzene, DIPEA, rt, 72%; (f) 1 N NaOH–H_2O, MeOH, 65 °C, 91%; (g) PS-tetrafluorophenol, *N,N′*-diisopropylcarbodiimide, DMAP, NMP; (h) pyrrolidine, DMF, rt; then PS-NCO, PS-MTBD, rt, 55% (two steps).

Table 1. Modification of the 2-substituted benzimidazole



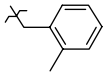
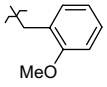
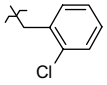
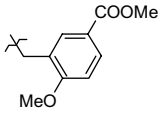
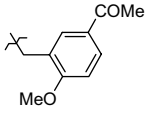
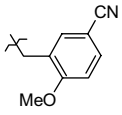
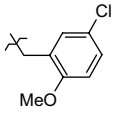
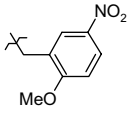
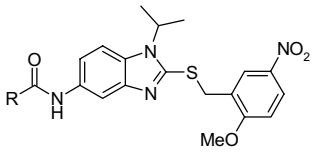
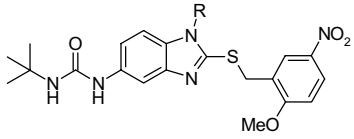
Compd	R	IC_{50} (μM)	
		r-LHRH	h-LHRH
7a		>10	3.2
7b		>10	2.1
7c		>10	6.3
7d		>10	0.98
7e		>10	0.26
7f		>10	0.57
7g		>10	0.16
7h		>8.2	0.28

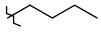
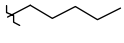
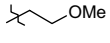
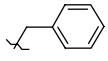
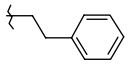
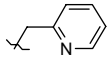
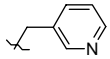
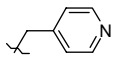
Table 2. Modification of the 5-substituted benzimidazole



Compd	R	IC_{50} (μM)	
		r-LHRH	h-LHRH
17a		0.71	0.88
18a		0.63	1.5
18b		1.5	0.25
18c		>10	0.18
18d		0.11	0.18
19a		0.062	0.062
19b		0.28	0.6
19c		>10	3.3
19d		1.6	1.9

Table 3. Modification of the N1-substituted benzimidazole

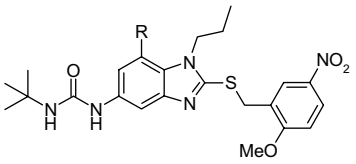


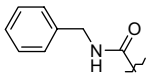
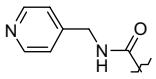
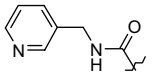
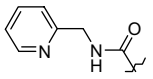
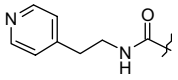
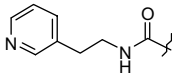
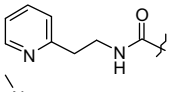
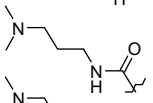
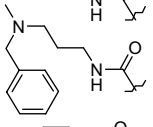
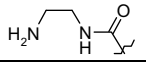
Compd	R	IC_{50} (μM)	
		r-LHRH	h-LHRH
12a		0.86	0.079
12b		0.17	0.042
12c		0.12	0.018
12d		0.33	0.023
12e		0.88	0.21
12f		0.28	0.057
12g		0.16	0.028
12h		0.3	0.36
12i		0.67	0.043
12j		0.15	0.033
12k		0.24	0.047
12l		>2.6	0.35

electron-donating substituents in the *ortho*-position and electron-withdrawing substituents in the *meta*-position, giving submicromolar antagonists of the human LHRH receptor. These compounds (**7a**–**h**), however, were inactive at the rat LHRH receptor, prohibiting rodent in vivo experiments.

We also investigated the SAR at the 5-position of the benzimidazole core (Table 2). Replacement of the cyclopropyl moiety of **7h** with cyclobutyl led to loss of activity for the human receptor (see compound **18a**). It was interesting that acyclic alkyl substituted analogs **18b**–**d** were found to have good potency. Furthermore, we were delighted to see that **18d** was potent against both rat and human receptors. This result prompted us to investigate the SAR of the acetamide further. Replacement of the methylene in the amide portion of **18d** with a heteroatom gave **17a** and **19a**. While *tert*-butyl carbamate **17a** was less potent, the corresponding urea **19a** was the first example of a double-digit nanomolar antagonist of both rat and human receptors in this series. The SAR observed among **17a**, **18d**, and **19a** clearly indicates the importance of two-hydrogen-bond donors for

Table 4. Modification of the 7-substituted benzimidazole



Compd	R	IC_{50} (μM)	
		r-LHRH	h-LHRH
23		0.28	0.037
24		0.51	0.021
26		0.140	0.610
26a		0.200	0.270
26b		0.023	0.041
26c		0.49	0.41
26d		0.13	0.12
26e		0.035	0.061
26f		0.054	0.069
26g		0.051	0.031
26h		0.045	0.13
26i		0.11	0.16
26j		0.056	0.027
26k		0.019	0.17
26l		0.021	0.19
26m		0.055	0.21

optimal interaction with the LHRH receptor. Further modification of the *tert*-butyl moiety in **19a** did not yield more potent analogs (see compounds **19b–d**). Therefore, compound **19a** was chosen for further investigations.

The SAR of the benzimidazole N-alkyl fragment was less restrictive (Table 3). In general, small alkyl substituted compounds **12a–f** showed good potency. With the exception of analog **12l**, replacement of the alkyl groups with aromatic substituents (**12g–k**) maintained potency. Within the series, however, the *n*-propyl analog **12c** was the most potent.

We also explored effects on introducing an additional substituent in the 7-position of the benzimidazole core (Table 4). We were delighted to find that the pyrrolidine amide analog **26** was still potent, despite its considerable structural modification. Replacement of the pyrrolidine moiety of **26** with dimethylamine maintained potency (see compound **26a**). Removal of one methyl moiety in **26a** even improved activity (see compound **26b**). The SAR observed among **26**, **26a**, and **26b** clearly indicates the importance of an amide NH for optimal interaction with the LHRH receptor. This result prompted us to investigate the SAR of the amide further. Oxygen derivatives **23** as well as **24** have good potency at the human receptor, but are less potent at the rat receptor. Within this series, **26b** was the another example of a double-digit nanomolar antagonist on both rat and human receptors. Therefore, we focused on the modification of mono alkyl amides. *tert*-Butyl amide analog **26c** showed a decrease in potency. Interestingly, the alkyl groups could be replaced with benzyl with only a slight loss in potency (see compound **26d**). Most known LHRH antagonists contain a basic moiety.[8] This inspired us to introduce several basic functionalities into our LHRH antagonists (see compounds **26e–m**). Indeed, the incorporation of the pyridine ring (**26e–j**) improved potency compared to **26d**. The introduction of tertiary or primary amines (**26k–m**) resulted in good activity for the rat LHRH receptor, but reduced potency against the human receptor.

Of all analogs, the *n*-propyl compound **12c** was the most potent functional antagonist on the human receptor (IC_{50} = 0.018 μM).[9] We confirmed the activity of **12c** by determining its binding constant to the human LHRH receptor (IC_{50} = 0.073 μM).[4]

4. Conclusion

We have identified a novel series of LHRH antagonists, represented by the *n*-propyl compound **12c**, with strong potency against both rat and human LHRH receptors. These SAR studies suggest that 1-(1*H*-benzimidazol-5-yl)-3-*tert*-butylurea is a new pharmacophore for small molecule LHRH antagonists.

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7. Typical procedure for preparing compound **26**; To a mixture of resin-bound active ester **25** (76 mg, 0.050 mmol, 0.66 mmol/g) in DMF (0.5 mL) was added pyrrolidine (0.0046 mL, 0.055 mmol) and the mixture was stirred overnight. PS-NCO (13 mg, 0.0125 mmol, 1 mmol/g) and PS-MTBD (5 mg, 0.0125 mmol, 2.6 mmol/g) were added to the suspension, which was stirred for 6 h. The resin was removed by filtration, and the filtrate was concentrated to give **26** (3.9 mg, 55% yield) as a colorless solid. Compound **26**: ^{1}H NMR (500 MHz, DMSO-*d*6) δ 0.74 (3H, t, J = 7.3 Hz), 1.30 (9H, s), 1.46 (2H, sextet, J = 7.3 Hz), 1.79 (2H, quintet, J = 6.9 Hz), 1.90 (2H, quintet, J = 6.9 Hz), 3.16 (2H, t, J = 6.9 Hz), 3.51 (2H, t, J = 6.9 Hz), 3.92 (2H, t, J = 7.3 Hz), 3.97 (3H, s), 4.60 (2H, s), 5.94 (1H, s), 7.25 (1H, d, J = 9.1 Hz), 7.25 (1H, d, J = 1.9 Hz), 7.51 (1H, d, J = 1.9 Hz), 8.20 (1H, dd, J = 2.8, 9.1 Hz), 8.26 (1H, s), 8.40 (1H, d, J = 2.8 Hz).
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9. Typical procedure for preparing compound **12c**: To a solution of 1-*tert*-butyl-3-(1-propyl-2-thioxo-2,3-dihydro-1*H*-benzimidazol-5-yl)-urea (**11**: R1 = –NH-*tert*-butyl, R2 = *n*-propyl) (18.0 mg, 0.06 mmol) in THF was added 2-(bromomethyl)-1-methoxy-4-nitrobenzene (28.9 mg, 0.12 mmol) and *N*,*N*-diisopropylethylamine (0.021 mL, 0.12 mmol). The resulting mixture was stirred at room temperature for 16 h. The solution was concentrated in vacuo. The crude residue was purified through preparative thin layer chromatography (AcOEt/Hex = 9/4) to give **12c** (21.0 mg, 76% yield) as a pale yellow solid. Compound **12c**: ^{1}H NMR (500 MHz, DMSO-*d*6) δ 0.78 (3H, t, J = 7.3 Hz), 1.3 (9H, s), 1.65 (2H, sextet, J = 7.3 Hz), 3.97 (3H, s), 3.99 (2H, t, J = 7.3 Hz), 4.58 (2H, s), 5.88 (1H, s), 7.10 (1H, dd, J = 1.6, 8.5 Hz), 7.24 (1H, d, J = 9.2 Hz), 7.31 (1H, d, J = 8.5 Hz), 7.63 (1H, d, J = 1.6 Hz), 8.15 (1H, s), 8.19 (1H, dd, J = 2.8, 9.2 Hz), 8.38 (1H, d, J = 2.8 Hz).