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Bioorganic & Medicinal Chemistry Letters 15 (2005) 805–807
Bioorganic & Medicinal Chemistry Letters

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

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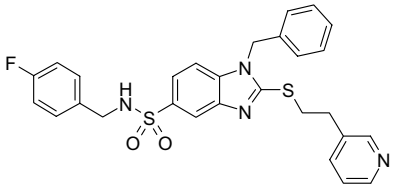
Received 3 September 2004; revised 28 October 2004; accepted 30 October 2004
Available online 21 November 2004

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** (IC_{50}: 4.2 nM).

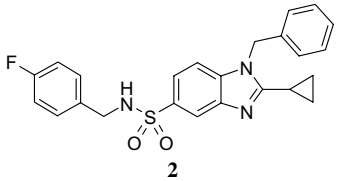
1. Introduction

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**, IC_{50} = 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).



1
IC_{50}=0.14 μM (rat-lhrh, Ca^{2+})
0.12 μM (human-lhrh, Ca^{2+})



2
IC_{50}=1.6 μM (rat-lhrh, Ca^{2+})
1.9 μM (human-lhrh, Ca^{2+})

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

2. Chemistry

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

Keywords: LHRH antagonist; Small molecule.
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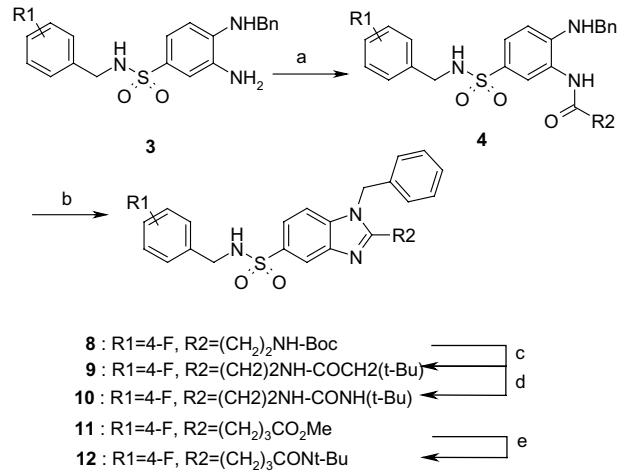
doi:10.1016/j.bmcl.2004.10.090



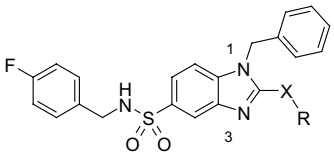
Scheme 1. Reagents and conditions: (a) RCO_2H, WSCI, HOBt, triethylamine, THF, rt, 90%; (b) compound **8**, HOAc, 90 °C, 70%, compound **11**, HOAc, 90 °C, 41%; (c) 4 N HCl, dioxane, rt, 99%, then, *tert*-butylacetyl chloride, triethylamine, CH_2Cl_2, rt, 38%; (d) 4 N HCl, dioxane, rt, 99%, then isocyanic acid *tert*-butylester, triethylamine, CH_2Cl_2, rt, 56%; (e) 1 N LiOH, THF, rt, 37%, then, *tert*-butylamine, WSCI, HOBt, triethylamine, THF, rt, 71%.

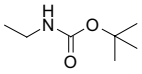
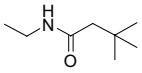
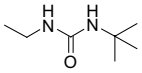
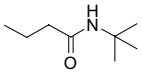
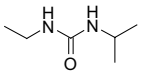
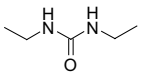
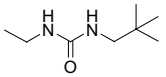
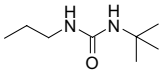
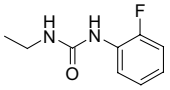
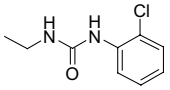
acid furnishing **9**. Diaminosulfonamide **3** was coupled and cyclized with glutaric acid monomethyl ester to give benzimidazole **11**. Hydrolysis and renewed amide formation furnished compound **12**.

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 IC_{50} 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 substitutents have been described by other groups.[4] Substituting the *tert*-butyl group with other alkyl substitutents 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**

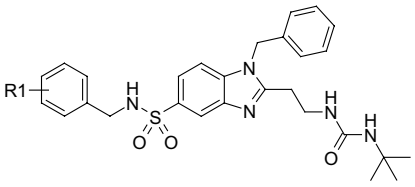


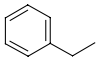
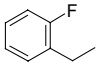
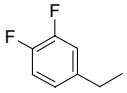
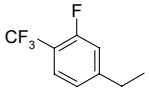
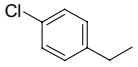
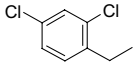
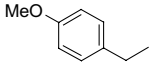
Cmpd	X	R	IC_{50} (μM)	
			r-lhrh	h-lhrh
5	CH_2	$-CH_2CH_3$	>10	>10
6	CHMe	$-CH_3$	0.69	0.39
7	CH_2	$-CH_2NH_2$	>10	>10
8	CH_2		0.54	0.74
9	CH_2		0.84	2.6
10	CH_2		0.012	0.020
12	CH_2		0.23	0.40
13	CH_2		0.079	0.15
14	CH_2		0.38	0.69
15	CH_2		0.030	0.11
16	CH_2		0.083	0.18
17	CH_2		0.053	0.066
18	CH_2		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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3. Fonseca, T.; Gigante, B.; Gilchrist, T. L. *Tetrahedron* **2001**, *57*, 1793. Typical procedure to prepare 2-[2-(3-*tert*-butyl-ureido)-ethyl]-1*H*-benzoimidazole-5-sulfonamide derivatives (synthesis of compound **10**): A solution of {2-[2-benzylamino-5-(4-fluoro-benzylsulfamoyl)-phenylcarbamoyl]-ethyl}-*tert*-butylcarbamate **4** (505 mg, 0.910 mmol) in 10 mL of acetic acid was heated at 90 °C for 3 h. After cooling to room temperature, the mixture was concentrated in vacuo, to give crude compound **8**. The crude mixture was diluted in 10 mL of CH_2Cl_2 and treated with 4 N 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 (100 mg, 0.210 mmol) was suspended in 1.5 mL of CH_2Cl_2. To the suspension was added triethylamine (0.0590 mL) and *tert*-butyl isocyanate (62.6 mg, 0.630 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 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*-butyl-ureido)-ethyl]-1*H*-benzoimidazole-5-(4-fluorobenzyl)sulfonamide **10** (70.7 mg, 63% yield for two steps) as a white precipitate. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.19 (9H, s), 2.95–2.98 (2H, t, J = 6.6 Hz), 3.44–3.47 (2H, t, J = 6.9 Hz), 3.93–3.94 (1H, d, J = 6.0 Hz), 5.56 (2H, s), 5.79 (1H, s), 5.83–5.85 (1H, t, J = 6.0 Hz), 7.04–7.07 (2H, t, J = 9.14 Hz), 7.11–7.13 (2H, d, J = 6.9 Hz), 7.24–7.35 (5H, m), 7.61–7.67 (2H, dd, J = 8.5 Hz, 21 Hz), 8.03–8.05 (2H, m).
4. Sasaki, S.; Cho, N.; Nara, Y.; Harada, M.; Endo, S.; Suzuki, N.; Furuya, S.; Fujino, M. *J. Med. Chem.* **2003**, *46*, 113.