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Syntheses and structure–activity relationship studies of piperidine-substituted quinolones as nonpeptide gonadotropin releasing hormone antagonists

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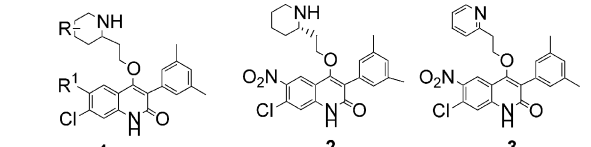
Abstract—Syntheses and structure–activity relationships of piperidine-substituted quinolones as nonpeptide gonadotropin releasing hormone antagonists are described. Some of substituents on the piperidine ring that were investigated included a fused phenyl group, a (6*R*)-trifluoromethyl group, (6*S*) and (6*R*)-methyl group. This study showed that GnRH binding potency was tolerated by a small group at the 6-position of the piperidine, and blocking the 6-position by a trifluoromethyl group reduced clearance rate and increased oral bioavailability.

Gonadotropin releasing hormone (GnRH) is a decapeptide released by the hypothalamus which binds to GnRH receptors on pituitary. The activation of this G-protein coupled receptor causes the release of luteinizing hormone, which regulate gonadal steroid hormone production.[1c,d] A variety of hormone disease conditions such as prostate cancer and endometriosis may be treated by suppression of the hypothalamic-pituitary–gonadal axis.

A series of recent reports from this laboratory describe the syntheses and structure–activity relationships of 3-aryl quinolones **1** as nonpeptide GnRH antagonists.[1] A cyclic amine moiety such as piperidine at the 4-position of the quinolone was found to contribute significantly to GnRH receptor binding affinity as demonstrated by the comparison of the piperidine analogue **2** and much less active pyridine compound **3**. Compounds with the (*S*)-configuration of cyclic amine at the 2-position were more potent in GnRH receptor binding than those with the *R* configuration.[1c] Previous work from this laboratory also showed that *N*-substituents on the piperidine ring could improve oral bioavailability but with reduced binding and functional activity.[1d] The effect of substitution on other positions of the piperidine ring on GnRH receptor binding and functional activity has not been previously reported. Here we describe the syntheses and structure–activity relationships of substituents on the piperidine ring in quinolone structure **1**.



Scheme 1 outlines the preparation of quinolone analogues **1**. 6-Nitro and 6-[*N*-(pyrimidin-6-yl)carboxamido]quinolones were prepared via the routes described in previous reports from this laboratory.[1a,c,e] Mitsunobu reaction of quinolones **4** with pyridinyl-, quinoliny- or isoquinolinylethanol followed by removal of the BOC

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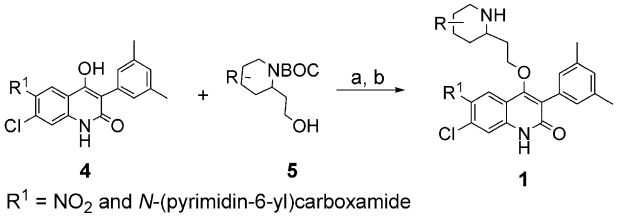


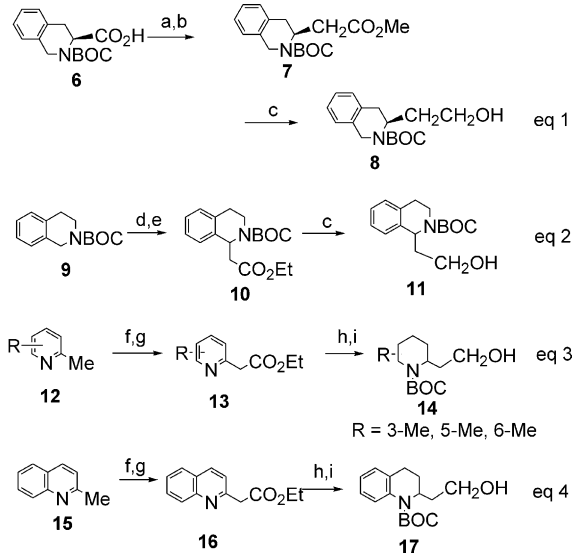
Scheme 1. Reagents and conditions: (a) DEAD, PPh_3, THF, 20 °C, 12 h; (b) TFA, CH_2Cl_2, anisolecat., 20 °C, 2 h.

group afforded the final compounds **1**. The R group in quinolones of type **1** includes fused-phenyl, methyl, ethyl, and trifluoromethyl groups.

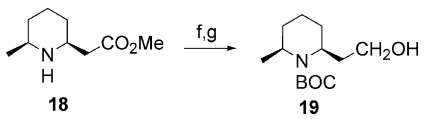
Scheme 2 shows the syntheses of (2-hydroxyethyl)-piperidines, quinoline and isoquinolines. 5,6-Phenyl-fused piperidine **8** was prepared as the (*S*)-enantiomer from (*S*)-tetrahydroquinoline carboxylic acid via the Arndt-Eistert homologation, followed by reduction of the subsequently formed ester (eq 1). Alcohols **11**, **14**, and **17** were synthesized by alkylation, followed by reduction or hydrogenation and subsequently reduction, (eqs 2–4).

The non-racemic 2-(methoxycarbonymethyl)-6-(*S*)-methylpiperidine **18** was prepared following a procedure of Munchhof and Meyers.[2] Reduction of ester **18** with lithium aluminum hydride followed by BOC-protection afforded **19** (Scheme 3).

In order to investigate the opposite steric effect of the 6-(*R*)-methyl substituent on the GnRH binding affinity, intermediate (2*S*)-(2-hydroxyethyl)-(6*R*)-methylpiperidine **23** was prepared by alkylation of the BOC-protected piperidine following the procedure of Beak and Lee.[3]



Scheme 2. Reagents and conditions: (a) $ClCO_2Bui$, TEA, THF/ether, 0 C, 1 h; and excess ethereal CH_2N_2, 0 °C, 3 h; (b) AgOBz (cat.), TEA, MeOH; 0–20 °C, 3 h; (c) $LiAlH_4$, Et_2O, 0 °C, 2 h; (d) *n*-BuLi, TMEDA, THF, −78 °C, 0.5 h; (e) $BrCH_2CO_2Et$, THF, −78 °C, 3 h; (f) 2.2 equiv LDA, TMEDA, THF, −78 °C, 1 h; (g) ClCOOEt, THF, −78 to 20 °C, 12 h; (h) PtO_2 cat., H_2 (45 psi), AcOH, 20 °C, 12 h; (i) $(BOC)_2O$, CH_2Cl_2, 20 °C, 5 h.



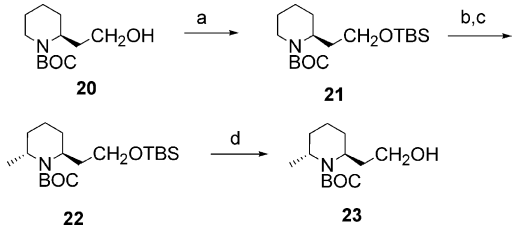
Scheme 3. Reagents and conditions: (f) $(BOC)_2O$, DMAPcat. CH_2Cl_2, 20 °C, 2 h; (g) $LiAlH_4$, ether, 0 °C, 2 h.

Treatment of compound **21**[1b] with *s*-butyllithium in ether at −20 °C followed by reaction with dimethylsulfate at −78 °C provided compound **22** in ca. 50% yield. The product thus obtained is exclusively the *trans* diastereomer based on ^1H NMR spectrum (Scheme 4).

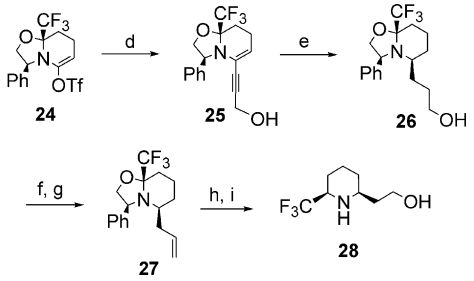
(2*S*)-(2-Hydroxyethyl)-(6*R*)-trifluoromethylpiperidine **28** was prepared from lactam triflate **24** that was discovered in our laboratory (Scheme 5).[4] Thus, reaction of triflate **24** with $PdCl_2(PPh_3)_2$ and propargyl alcohol gave the coupled product **25**. Subsequent hydrogenation of the enamine double bond and the triple bond over platinum oxide in toluene afforded a single diastereomer **26**. Removal of one carbon unit from the 3-hydroxypropyl substituent via an elimination/ozonolysis strategy followed by hydrogenation gave alcohol **28**.

It is noteworthy that the earlier procedure of Munchhof and Meyers[2] failed to generate (2*S*)-(2-hydroxyethyl)-(6*R*)-trifluoromethylpiperidine **28**.[5]

Compounds were evaluated for their ability to compete with GnRH receptor agonist [^{125}I]buserelin for binding to the human GnRH receptor in the presence of 0.1% BSA. In addition, functional antagonism in vitro was determined via inhibition of GnRH-stimulated phosphatidyl inositol (PI) hydrolysis by cloned Chinese hamster ovary (CHO) cells stably expressing the human GnRH receptor.[1c,d]



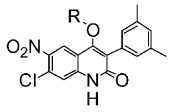
Scheme 4. Reagents and conditions: (a) TBSCl, pyridine, CH_2Cl_2, 0–20 °C, 12 h; (b) *s*-BuLi, TMEDA, −78 °C to −18 °C, 0.5 h; (c) $(MeO)_2SO_2$, −78 °C to −20 °C, 4 h; (d) aq HF, 20 °C, 12 h.

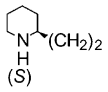
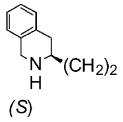
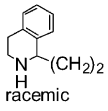
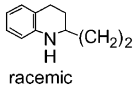
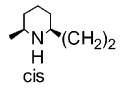
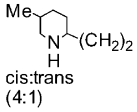
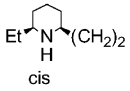
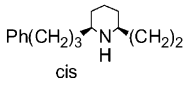


Scheme 5. Reagents and conditions. (d) $PdCl_2(PPh_3)_2$, CuI, propargyl alcohol, *i*-Pr_2NH, THF, 20 °C, 12 h; (e) PtO_2 cat., H_2 (50 psi), toluene, 18 h; (f) 2-cyanoseleno-nitrobenzene, $BuPh_3$, THF, 0–20 °C, 2 h; (g) H_2O_2, 0–20 °C; (h) O_3, MeOH, –78 °C, 15 min and Me_2S, 20 °C, 12 h; (i) $Pd(OH)_2$ cat., H_2 (50 psi), EtOH, 20 °C, 12 h.

In order to investigate the effect of an aromatic ring around the piperidine ring on the GnRH binding, phenyl fused quinolined and isoquinolines **30**–**32** were evaluated for the rat GnRH binding. In this series the fused phenyl group at the 4,5-position (compound **30** in Table 1) resulted in 7-fold loss of binding affinity at the rat GnRH receptor as compared to the parent compound **29**. When the fused phenyl was moved closer to the 2-hydroxyethyl group at the 2-position of the piperidine ring (**31**), binding affinity at the rat receptor was reduced by more than 30-fold. In addition, moving the fused phenyl away from the 2-position to 5,6-position of the piperidine ring (**32**) also led to a big loss of the binding affinity. These results indicated that a phenyl group fused to the piperidine rings resulted in reduced binding activity at the rat GnRH receptor.

Table 1. Inhibition of rat GnRH receptor binding by quinolones with a 6-alkyl-substituted piperidine



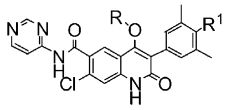
Compd	R	rGnRH (IC_{50})
29[1b]		10 nM
30		70 nM
31		750 nM
32		85% inh. @10.0 μM
33		15 nM
34		63 nM
35		45 nM
36		18 nM
37		400 nM

Tolerability of the binding potency to substituents on the piperidine ring was further investigated with analogues containing a 3-, 5-, or 6-methyl group. The methyl group at the 3- (**35**) or 5-position (**34**) resulted in a slight reduction in binding affinity. In contrast, the 6-methyl (**33**) and the 6-ethyl group (**36**) derivatives were equipotent to **29**. However, 6-(3-phenyl)propyl substituent led to more than 20-fold reduced binding affinity as compared to the parent compound **29**.

Results from Table 1 showed that potency of the rat GnRH binding was tolerated only by a small substituent at the 6-position of the piperidine ring. Based on these results, study was focused on 6-substituted analogues.

Table 2 lists quinolone-6-carboxamide compounds with either a 6-methyl a 6-trifluoromethyl or a 6-ethyl substituted piperidine. Compounds with (6*S*)-methyl (**40**) and (6*R*)-methyl (**41**) are both very potent antagonists at the human GnRH receptor as compared to the parent compound **38**, suggesting that stereochemical configuration at the 6-position of the piperidine ring has no effect on either GnRH binding or functional activity. (6*R*)-Trifluoromethyl group resulted in about 7-fold reduction of binding and functional activity (compounds **43** vs **42**). The trifluoromethylated compound **43** was almost equipotent to the 6-ethyl substituted compound

Table 2. Inhibition of human GnRH receptor binding and PI turnover by quinolones with a 6-alkyl-substituted piperidine



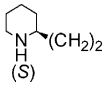
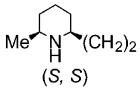
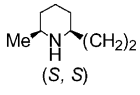
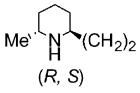
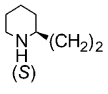
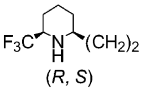
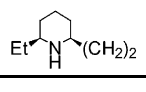
Compd	R	R^1	hGnTH (IC_{50})	PI Turn (IC_{50})
38[1e]		H	0.9 nM	5.0 nM
39		Me	0.6 nM	9.8 nM
40		H	0.5 nM	8.7 nM
41		H	0.5 nM	11.5 nM
42[1e]		Me	0.3 nM	2.2 nM
43		Me	2 nM	18 nM
44		H	5.7 nM	—

Table 3. Clearance rate and oral bioavailability of compounds **42** and **43**

Compd	Clearance rate in dog (mL/Kg/min)	F% in dog
42	36.8	4.4
43	21.6	14.6

44 in binding, although 2-(2-hydroxyethyl)-6-trifluoromethyl piperidine is about one thousand-fold less basic than piperidine ($pK_a = \sim 9$ for piperidine versus $pK_a = 5.6$ for 2-(2-hydroxyethyl)-6-trifluoromethyl) piperidine **28**[6]). Therefore, basicity of the cyclic amine has no significant effect on the GnRH binding affinity.

Although the previously reported compound **42**, without 6-substituent, was still the most active GnRH binding, it showed low oral bioavailability and high clearance in dogs. Considering that the high clearance might relate to metabolism at the 6-position of the piperidine, pharmacokinetic properties in dog of 6-trifluoromethyl piperidine derivative **43** were evaluated and compared to the parent compound **42**. Indeed, the 6-trifluoromethyl group increased the oral bio-availability (F%) by 3-fold and reduced the clearance rate by about 2-fold (Table 3).

In conclusion, we have synthesized a variety of novel quinolone analogues with substituted piperidines. SAR studies indicated that adding a substituent on the piperidine ring did not enhance GnRH binding affinity or functional activity, although installing a relatively small substituent at the 6-position was tolerated. Basicity of the cyclic amine and stereochemical configuration of substituents at the 6-position of the piperidine had no significant affect on potency of the GnRH receptor binding. Comparison of the pharmacokinetic results of trifluoromethyl substituted antagonist **43** with those of the parent compound **42** showed that modification of the piperidine could improve oral bioavailability.

References and notes

1. (a) DeVita, R. J.; Hollings, D. D.; Goulet, M. T.; Wyvratt, M. J., Jr.; Fisher, M. H.; Lo, J.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2615. (b) DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J., Jr.; Fisher, M. H.; Lo, J.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2621. (c) DeVita, R. J.; Walsh, T. F.; Young, J. R.; Jiang, J.; Ujjainwalla, F.; Toupence, R. B.; Parikh, M.; Huang, S. X.; Fair, J. A.; Goulet, M. T.; Wyvratt, M. J.; Lo, J.; Ren, N.; Yudkovitz, J. B.; Yang, Y. T.; Cheng, K.; Cui, J.; Mount, G.; Rohrer, S. P.; Schaeffer, J. M.; Rhodes, L.; Drisko, J. E.; McGowan, E.; MacIntyre, D. E.; Vincent, S.; Carlin, J. R.; Cameron, J.; Smith, R. G. *J. Med. Chem.* **2001**, *44*, 917. (d) Walsh, T. F.; Toupence, R. B.; Young, J. R.; Huabg, S. X.; DeVita, R. J.; Hollings, D. D.; Goulet, M. T.; Wyvratt, M. J., Jr.; Fisher, M. H.; Lo, J.; Cui, J.; Ren, N.; Yudkovitz, J. B.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 443. (e) Young, J. R.; Huang, S. X.; Chen, I.; Ren, N.; Walsh, T. F.; DeVita, R. J.; Hollings, D. D.; Wyvratt, M. J., Jr.; Goulet, M. T.; Ren, N.; Lo, J.; Yang, Y. T.; Yudkovitz, J. B.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1723.
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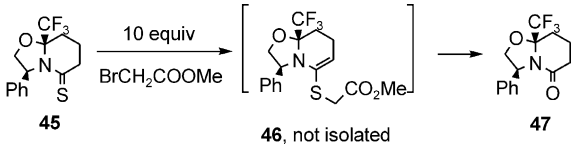
3. Beak, P.; Lee, W. K. J. *Org. Chem.* **1990**, *55*, 2578.
4. Jiang, J.; DeVita, J. R.; Doss, G. A.; Goulet, M. T.; Wyvratt, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 593.
5. In attempts to apply the procedure of Munchhof and Meyers to preparation of compound **28**, intermediate **46** was not detected by ^1H NMR, and only compound **47** was isolated. Intermediate **46** was presumably hydrolyzed by a trace amount of water in methyl α-bromoacetate.



6. We thank Dorothy Levorse for testing basicity of compound 2-(2-hydroxyethyl)-6-trifluoromethylpiperidine (**28**).