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Zwitterionic uracil derivatives as potent GnRH receptor antagonists with improved pharmaceutical properties

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ABSTRACT

A novel series of potent zwitterionic uracil GnRH antagonists were discovered that showed reduced liability for CYP3A4 enzyme inhibition.

The potential of non-peptide Gonadotropin-releasing hormone (GnRH) receptor antagonists serving as novel therapeutics for hormone-dependent disease states such as prostate cancer, endometriosis, and benign prostate hyperplasia has led to discovery of a wide range of small molecule antagonists.[1,2] We have reported that uracil-based analogs are potent GnRH receptor antagonists based on in vitro and in vivo characterizations.[3] However, CYP3A4 inhibition was a common issue for early uracil analogs that contained a basic amine such as **1** in Figure 1. Since inhibition of CYP3A4 enzyme is well known to potentially induce drug–drug interactions, elimination of such undesired property from this class of molecules was clearly necessary. Recently, we have shown[4] that addition of an acid can drastically reduce the possibility of this class of molecules to inhibit CYP3A4 enzyme activity regardless of the location of the acid. However, the GnRH receptor-binding affinity was heavily dependent on the exact location of this acidic functional group. For example, the acid linked to the phenyl group at the right hand side of the molecule (**2b**) diminishes the GnRH receptor-binding affinity compared to its ester precursor (**2a**), yet the acid attached to the amine group through a propylene chain (**3b**) is highly potent GnRH receptor binder. As a matter of fact, such combination of the amino and acid functionalities offered similar potency to its amine precursor **1**, yet without the CYP3A4 liability. Interestingly, such zwitterionic molecules show good oral bioavailability in cynomolgus monkeys, albeit relatively poor exposure in rats.[4] To further expand the SAR on zwitterionic uracils, we report here a novel way of linking an acid group to the 5-phenyl uracils, which generated a series of novel and potent zwitterionic molecules without inhibition of CYP3A4 enzyme.

The initial syntheses of such molecules are outlined in Scheme 1. The starting compounds (**4a**–**d**)[3,4] were first treated with BBr_3 to remove the methyl group; subsequently, the amino group was protected using Boc_2O to give compounds **5a**–**d**. Alkylation with $Br(CH_2)_nCO_2Et$, followed by hydrolysis of the ethyl ester and removal of the Boc protecting group, yielded the desired zwitterionic compounds **6a**, **6b**, **7a**–**c**, **8a**–**c**, **8e**, and **9a**. Compound **8d** was prepared alternatively according to Scheme 2 where **5c** was first alkylated with 3-bromopropanol, followed by the oxidation of the hydroxyl group to the corresponding carboxylic acid functionality and then removal of the Boc-protecting group. These compounds were assayed against the human GnRH receptor binding, IP_3 function, and CYP3A4 inhibition.[6] The results are summarized in Table 1. Our previous SAR has indicated that polar group cannot be tolerant around the 3-methoxylphenyl region at 5-uracil, thus our campaign to introduce the acid functionality on 3-methoxyphenyl

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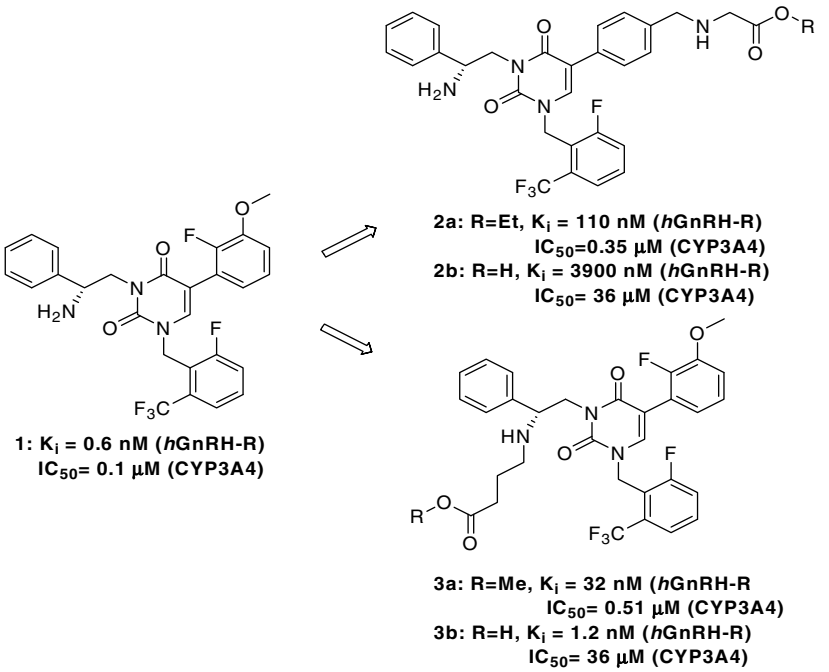
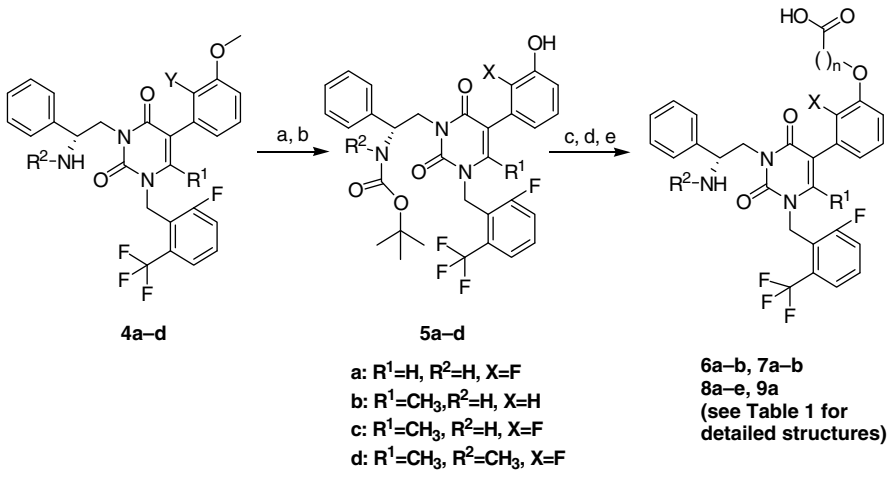
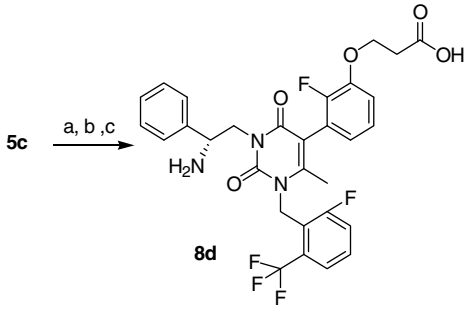


Figure 1. Structures and biological activities of previously reported compounds **1**–**3**.



Scheme 1. Reagents and condition: (a) BBr_3, DCM, −78 °C; (b) Boc_2O, DCM, Et_3N; (c) K_2CO_3, DMF, $Br(CH_2)_nCO_2Et$; (d) LiOH, THF/water; (e) TFA/DCM.



Scheme 2. Reagents and condition: (a) K_2CO_3, DMF, $BrCH_2CH_2CH_2OH$, 50 °C; (b) cat. $RuCl_3$, $NaIO_4$, DCM, MeCN, H_2O; (c) TFA/DCM.

position of compound **1** initialized with a long alkyl-acid such as pentanoic acid (**6a**), which yielded moderate but encouraging activity (K_i = 34 nM); the longer acid **6b** did not improve the activity. Both compounds, as we expected, did not exhibit significant CYP3A4 inhibition. To search for an improvement on GnRH activity, we turned our attention to modify on more potent analogs (**4b**–**d**). Indeed, compound **7a**, 6-methyluracil analog based on **4b**, was much more potent (K_i = 2.1 nM) than that of the non-methyl analog **6a**. However, shortening the chain length (**7b** and **7c**) decreased the potency slightly. Historically, addition of a fluoro group to the 3-methoxyphenyl ring of **4b** further enhances the GnRH activity. Therefore, compounds **8a**–**e** were prepared accordingly. Enhancement of the potency by fluoro group was not clearly observed in the binding assay, but was well displayed in the functional assay which measures the ability of a compound to inhibit GnRH-stimulated [^{3}H] inositol phosphate hydrolysis. Overall, fluoro analogs were about 5–10 times more potent than the corresponding non-fluoro analogs (such as **8a** and **8b** vs **7a** and **7b**). Because of their low possibility of CYP3A4 inhibition and potent GnRH antagonistic activity, pharmacokinetic studies of several