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Synthesis and structure–activity relationships of uracil derived human GnRH receptor antagonists: (*R*)-3-[2-(2-amino)phenethyl]-1-(2,6-difluorobenzyl)-6-methyluracils containing a substituted thiophene or thiazole at C-5

Martin W. Rowbottom,[a,*] Fabio C. Tucci,[a] Patrick J. Connors, Jr.,[a] Timothy D. Gross,[a] Yun-Fei Zhu,[a] Zhiqiang Guo,[a] Manisha Moorjani,[a] Oscar Acevedo,[a] Lee Carter,[b] Susan K. Sullivan,[b] Qiu Xie,[c] Andrew Fisher,[d] R. Scott Struthers,[c] John Saunders[a] and Chen Chen[a,*]

[a]*Department of Medicinal Chemistry, Neurocrine Biosciences Inc., 12790 El Camino Real, San Diego, CA 92130, USA*
[b]*Department of Pharmacology, Neurocrine Biosciences Inc., 12790 El Camino Real, San Diego, CA 92130, USA*
[c]*Department of Endocrinology, Neurocrine Biosciences Inc., 12790 El Camino Real, San Diego, CA 92130, USA*
[d]*Department of Preclinical Development, Neurocrine Biosciences Inc., 12790 El Camino Real, San Diego, CA 92130, USA*

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Abstract—The synthesis of a series of (*R*)-3-[2-(2-amino)phenethyl]-1-(2,6-difluorobenzyl)-6-methyluracils containing a substituted thiophene or thiazole at C-5 is described. SAR around C-5 of the uracil led to the discovery that a 2-thienyl or (2-phenyl)thiazol-4-yl group is required for optimal receptor binding. The best compound from the series had a binding affinity of 2 nM (K_i) for the human GnRH receptor. A novel and convenient preparation of *N*-1-(2,6-difluorobenzyl)-6-methyluracil is also described.
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Gonadotropin-releasing hormone (GnRH) is a decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2) produced and secreted by the hypothalamus and which interacts with specific GnRH receptors located within the anterior pituitary, releasing both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from this site.[1,2] A number of disease states including endometriosis, uterine fibroids, and prostate cancer can be controlled via the suppression of GnRH stimulated release of both FSH and LH. This may be clinically achieved via agonism or antagonism of the GnRH receptor and a number of peptide agonists and antagonists are currently available as represented by Leuprorelin®[3] and Cetrotide™,[1] respectively. However, due to the very low oral bioavailability of these peptides, administration is normally via injection or depot formulation. In addition, treatment with agonists initially leads to the overproduction of both FSH and LH with a concomitant 'flare effect', which tends to exacerbate symptoms (in the short term) in patients. In response to the need for a more convenient and clinically flexible route of administration, intensive efforts have been initiated toward the development of orally bioavailable small-molecule GnRH antagonists.[4–6]

Previously we have reported the discovery of a new class of uracils as orally bioavailable human GnRH [hGnRH] receptor antagonists, exemplified by 3-(2-aminoethyl)-5-aryl-6-methyluracils **1** (Fig. 1).[5] Subsequent modification of the substituent at N-3, led to the discovery of highly potent (*R*)-3-[2-(2-amino)phenethyl]-5-aryl-6-methyluracils **2**.[6] Furthermore, chemistry was developed which allowed for facile variation of the N-1 substituent (of the uracil ring) and we were able to show that the inclusion of an electron-deficient 2,6-disubstituted benzyl group (represented by **3**) was optimal for hGnRH receptor binding.[6] Previously, we have only described uracils containing a substituted phenyl ring at C-5 (**1**

* Corresponding authors. Tel.: +1-858-658-7799; fax: +1-858-658-7601; e-mail: mrowbottom@neurocrine.com

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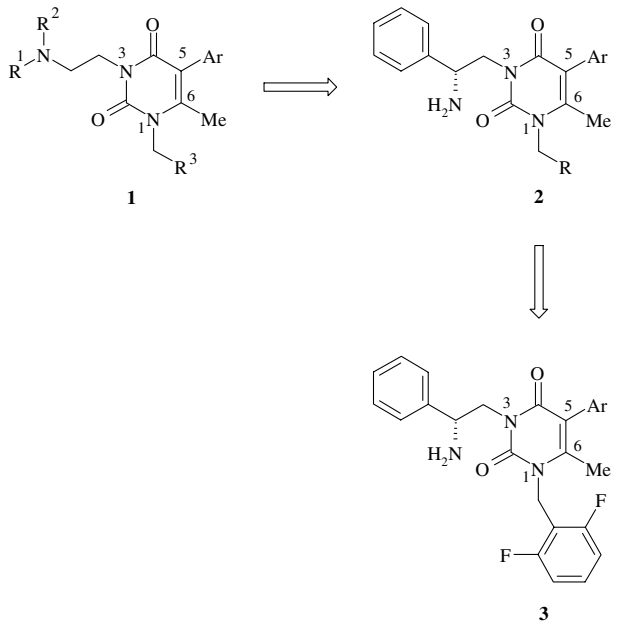
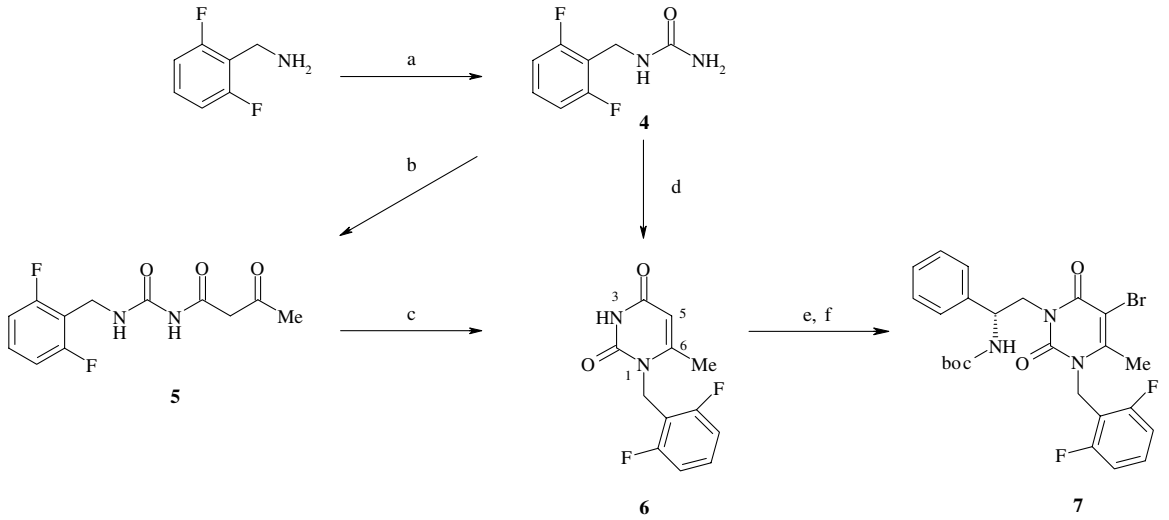


Figure 1. General structures of uracil based GnRH antagonists.

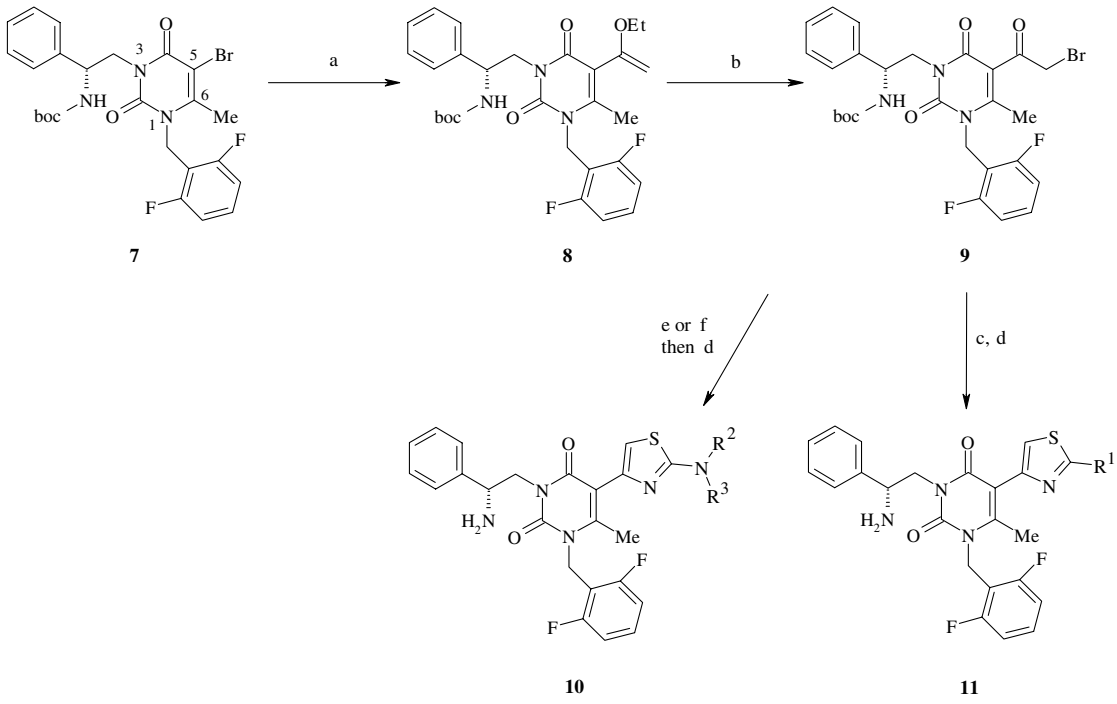
and **2**). We also wanted to incorporate substituted heteroaryl rings at this position, with the hope of discovering further potent analogs with different pharmacokinetic and metabolism properties. In this letter we wish to report the synthesis and hGnRH activity of several (*R*)-*N*-3-[2-(2-amino)phenethyl]-1-(2,6-difluorobenzyl)-6-methyluracils **3**, containing a substituted thiophene or thiazole ring at C-5.

(*R*)-*N*-3-[2-(2-Amino)phenethyl]-1-(2,6-difluorobenzyl)-5-aryl-6-methyluracil analogs **3** were prepared from (*R*)-*N*-3-[2-(2-amino)phenethyl]-5-bromo-1-(2,6-difluorobenzyl)-6-methyluracil **7** (Scheme 1), which in turn was obtained from *N*-1-(2,6-difluorobenzyl)-6-methyluracil **6**. Reaction of urea with diketene to give 6-methyluracil via a two-step process has previously been reported.[7] We have shown that reaction of (2,6-difluorobenzyl)urea **4** with diketene in pyridine at ambient temperature gave *N*-acetoacetylurea **5** (isolated in 60% yield), which upon refluxing in acetic acid for 1 h gave uracil **6** in 95% yield (Scheme 1).[5b,d] However, the fact that the preparation of uracil **6** (from urea **4**) still involved two separate steps and the overall yield was below 60%, encouraged us to develop a more efficient route. Yamamoto et al. have reported that reaction of primary amides with diketene in the presence of trimethylsilyl iodide (generated in situ from trimethylsilyl chloride and sodium iodide) gave *N*-acetoacetylcarboxamides in high yield.[8] We reasoned that in a similar manner the reaction of urea **4** with diketene (in the presence of trimethylsilyl iodide) should give **5**. More importantly, **5** should undergo the acid catalyzed cyclodehydration step in situ (mediated by the hydrogen iodide generated in the reaction) to produce **6** in one step. Gratifyingly, the reaction of urea **4** with diketene in the presence of trimethylsilyl iodide, gave uracil **6** as the only product in 93% yield.[9,10] Bromination of **6** (bromine in acetic acid) followed by N-3 alkylation with (*R*)-*N*-boc-2-phenylglycinol (via a Mitsunobu protocol) gave 5-bromouracil **7** in 63% yield (over two steps).

5-(Thiazol-4-yl)-6-methyluracil derivatives **10** and **11** (Scheme 2 and Tables 1, 2) were prepared directly from α-bromoketone **9**. The reaction of **7** with tri-*n*-butyl-(1-ethoxyvinyl)tin via a Stille-coupling[11] gave ethylvinyl ether **8**, which upon treatment with NBS in H_2O/THF gave bromoketone **9** in 40% yield (over two steps). Substituted thiazole rings are easily prepared via the Hantzsch thiazole reaction, in which thioureas or thioamides are condensed with α-bromoketones.[12] The reaction of bromoketone **9** with a variety of thioureas or thioamides followed by *N*-Boc deprotection gave 5-(thiazol-4-yl)-6-methyluracils **10**(**a**, **b**, **d**, **e**, **g**–**m**) and



Scheme 1. Reagents and conditions: (a) urea, water, HCl, reflux, 79%; (b) diketene, pyridine, rt, 24 h, 60%; (c) AcOH, reflux, 1 h, 95%; (d) diketene, trimethylsilyl chloride, sodium iodide, MeCN, 5 °C to rt, 20 h, 93%; (e) Br_2, AcOH, rt, 1 h, 88%; (f) (*R*)-*N*-Boc-2-phenylglycinol, DEAD, PPh_3, THF, rt, 12 h, 71%.



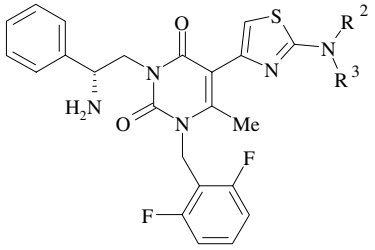
Scheme 2. Reagents and conditions: (a) tri-*n*-butyl(1-ethoxyvinyl)tin, $Pd(PPh_3)_4$, 1,4-dioxane, reflux, 12 h; (b) NBS, THF/H_2O, rt, 4 h, 40% (from **7**); (c) $R^1C(=S)NH_2$, EtOH, reflux, 2–3 h; (d) TFA, DCM, rt, 1 h; (e) $R^2R^3NC(=S)NH_2$, EtOH, reflux, 2–3 h; (f) ammonium thiocyanate, R^2R^3NH, EtOH, reflux, 13 h.

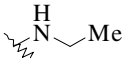
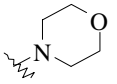
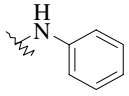
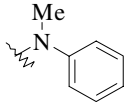
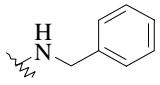
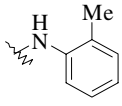
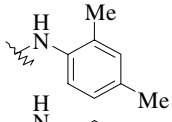
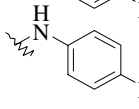
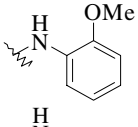
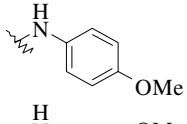
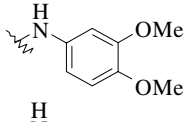
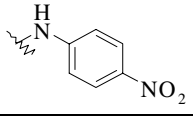
11(a–m), respectively (Scheme 2 and Tables 1, 2).[13] Alternatively, treatment of α-bromoketones with thiocyanate salts followed by the addition of a primary or secondary amine, gives 2-aminothiazoles in one pot.[14] The reaction of bromoketone **9** with ammonium thiocyanate and amines (followed by *N*-Boc deprotection), gave 5-(thiazol-4-yl)-6-methyluracils **10** (**c**, **f**) (Scheme 2 and Table 1).[15] 5-(2-Thienyl)-6-methyluracil derivatives **12** may be prepared in two steps from bromouracil **7** via a Suzuki coupling with 2-thienylboronic acids, followed by an *N*-Boc deprotection (Scheme 3 and Table 3).

All 5-thiazolyl and 5-thienyl-6-methyluracils described (Tables 1–3) were assayed for their ability to bind competitively to the cloned hGnRH receptor expressed in RBL cells, using a 96-well filtration apparatus[16,17] and ^{125}I-[His^5, D-Tyr^6]GnRH as the radiolabeled ligand.[18] The functional antagonism of the described compounds was confirmed by their ability to inhibit GnRH-stimulated Ca^{2+} flux in the transfected cells in a dose-dependent manner.[4g,19] Activity in the 5-(thiazol-4-yl)uracil series was dependent upon the nature of the thiazole ring substituent. Thus polar functional groups (**10a**, **c**, Table 1) were less tolerated by the receptor than those containing more lipophilic substituents. For instance, 2-(ethylamino)thiazole derivative **10b** had a K_i of 270 nM, which was approximately 10-fold more potent than the unsubstituted aminothiazole **10a** (which had a K_i of 3000 nM) and 5-fold more potent than the 2-(morpholino)thiazole derivative **10c** (with a K_i of 1500 nM). Binding affinity was further increased by the incorporation of either a 2-aminophenyl (**10d**, K_i of 70 nM), 2-(methylamino)phenyl (**10e**, K_i of 34 nM), or benzyl group (**10f**, 35 nM). Because of the affinity of **10d**, and that we suspected **10d** would be metabolically more stable than the N-methylated and *N*-benzyl analogs (**10e** and **10f**, respectively), other compounds containing a substituted *N*-phenyl ring were prepared (**10g–m**). It was observed that a 4-substituent in the phenyl ring largely maintained activity whilst 2-substituents were not acceptable. For example, 2-(2-methoxylphenyl)aminothiazole **10j** (K_i of 130 nM) was less potent than the corresponding 4-methoxy derivative **10k** (K_i of 42 nM) or the unsubstituted derivative **10d** (K_i of 70 nM). These data may suggest that the presence of a ring substituent *ortho* to the nitrogen prevents the ring adopting a more planar orientation (with respect to the amino substituent), which may be required for optimal binding. The addition of a second methoxy group at position 3 (**10l**, K_i of 33 nM) was tolerated though did not improve potency. The replacement of the 4-methyl (**10i**, K_i of 49 nM) or 4-methoxy groups (**10k**) by a nitro group (**10m**) reduced potency approximately 3-fold (**10m** had a K_i of 160 nM).

Removal of the 2-amino functionality of the thiazole ring increases the lipophilicity of these compounds (relative to the amino derivatives), which we reasoned might improve potency. 5-(2-Methylthiazolyl)-6-methyluracil **11a** had a K_i of 120 nM (Table 2). Incorporation of the more lipophilic phenyl (**11b**) or benzyl group (**11c**) improved potency by approximately 5- and 13-fold to 26 and 9 nM, respectively. As with aminothiazole derivatives **10**, 4-substituted phenyl rings (**11d**, **f–h**, **j–l**) were preferred over those containing a 2- or 3-substituent. 4-(Trifluoromethyl)phenyl derivative **11d** (K_i of 47 nM) was 3-fold more potent than the corresponding 3-substituted analog **11e** (K_i of 150 nM). Similarly,

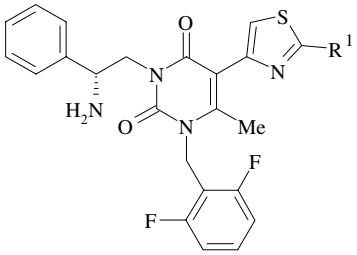
Table 1. Binding affinities of 5-(2-aminothiazol-4-yl)-6-methyluracils **10a–m** toward the hGnRH receptor

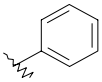
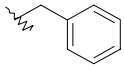
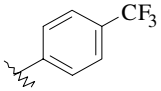
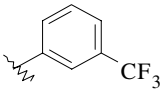
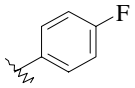
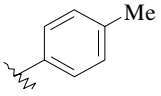
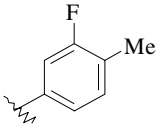
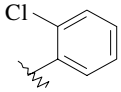
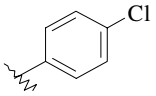
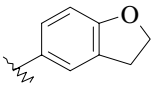
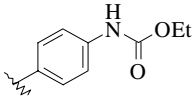
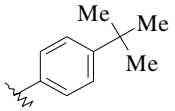


Compd	NR^2R^3	K_i (nM)[a]
10a		3000
10b		270
10c		1500
10d		70
10e		34
10f		35
10g		210
10h		130
10i		49
10j		130
10k		42
10l		33
10m		160

[a] Data are average of three or more independent measurements.[17]

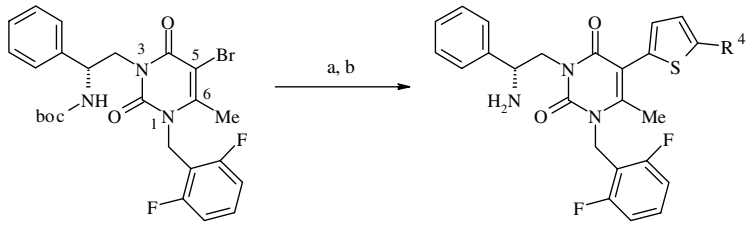
Table 2. Binding affinities of 5-(thiazol-4-yl)-6-methyluracils **11a–m** toward the hGnRH receptor



Compd	R^1	K_i (nM)[a]
11a		120
11b		26
11c		9
11d		47
11e		150
11f		42
11g		18
11h		49
11i		30
11j		15
11k		20
11l		7
11m		500

[a] See footnote to Table 1.

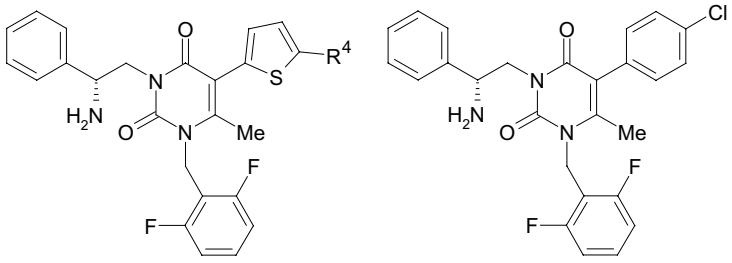
2-(4-chlorophenyl)thiazole **11j** (K_i of 15 nM) was 2-fold more active than the 2-chloro derivative **11i** (K_i of 30 nM). However, there seems to be a limitation as to the steric bulk tolerated. The 4-*tert*-butylphenyl analog **11m** had a K_i of 500 nM, which was over 20-fold less potent than the 4-methylphenyl derivative **11g**, which had a K_i of 18 nM. Surprisingly the *N*-carbamoyl derivative



7 12

Scheme 3. Reagents and conditions: (a) thiopheneboronic acid, $Pd(PPh_3)_4$, aq $Ba(OH)_2$, DME/PhH/EtOH, 90 °C, 15 h; (b) TFA, DCM, rt, 1 h.

Table 3. Binding affinities of 5-(2-thienyl)-6-methyluracils **12a–c** and 5-(4-chlorophenyl)-6-methyluracil **13** toward the hGnRH receptor



12a-c 13

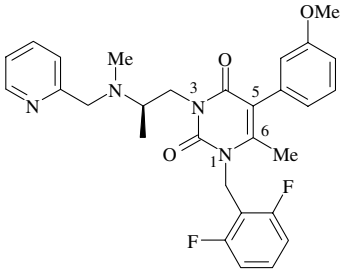
Compd	R^4	K_i (nM)[a]
12a	H	10
12b	Me	3
12c	Cl	2
13	—	14

[a] See footnote of Table 1.

11l had a K_i of 7 nM, this being the most potent analog of the thiazole series. Inclusion of a 2-thienyl group at C-5 of the uracil ring was also investigated (compounds **12a–c**, Table 3). The unsubstituted 2-thienyl derivative **12a** had a K_i of 10 nM and was already equipotent to thiazole derivative **11l**. Incorporation of a 5-methyl (**12b**) or 5-chloro substituent (**12c**) improved potency further (with measured K_i's of 3 and 2 nM, respectively). When compared directly to the corresponding 5-(4-chlorophenyl)-6-methyluracil derivative **13**[20] (Table 3) which had a K_i of 14 nM, compound **12c** displayed 7-fold greater affinity toward the receptor, thus demonstrating that the 5-phenyl group (of the uracil ring) can be replaced and potency maintained.

We were also interested in the overall metabolic stability of compounds described. Incubation with human liver microsomes (HLM) can be used to help estimate how much of a target compound will be removed by hepatic first-pass metabolism in vivo. For instance in an in vitro HLM assay,[5d] 5-(thiazol-4-yl)-6-methyluracils **11g** and **11j** (Table 2) had an intrinsic clearance of 36 and 46 mL/min/kg, respectively. When directly compared to (*R*)-1-(2,6-difluorobenzyl)-5-(3-methoxyphenyl)-3-(2-(*N*-methyl-*N*-(2-pyridyl)methyl)aminopropyl)-6-methyluracil **14**[5b] (Fig. 2) (a potent example from the first generation of uracil hGnRH antagonists), these compounds proved to be much more stable. In the same assay, uracil **14** had an intrinsic clearance of 1700 mL/min/kg.

Overall these data suggest that the substituent at C-5 of the uracil core lies in a relatively lipophilic area of the binding pocket. Uracils incorporating a 2-thienyl ring (at C-5) are generally preferred over the more polar thiazol-4-yl containing derivatives (compare compounds **11a** and **12b**).[21] Though as previously described, by increasing the lipophilic nature of the thiazole containing substituent, potency is much improved (compare **11a** with **11b**,**c**). We believe that this increase in lipophilicity does not adversely affect metabolic stability, as we have highlighted examples with an improved in vitro stability profile (toward HLM), when compared to potent first generation uracil antagonists. We also



14

K_i (hGnRH) = 5 nM

Figure 2. Structure of uracil derivative **14**.

speculate that this area of the binding pocket, which accommodates the C-5 substituent, is relatively open and able to tolerate somewhat larger functional groups (such as 2-phenyl or 2-benzylthiazol-4-yl moieties).[22]

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10. Experimental procedure for the preparation of *N*-1-(2,6-difluorobenzyl)-6-methyluracil **6**. Into a multi-neck 5 L flask fitted with a thermometer, dropping funnel and mechanical stirrer was placed 2,6-difluorobenzylurea **4** (100 g, 537 mmol), sodium iodide (121 g, 806 mmol), and dry acetonitrile (1 L). The reaction mixture was stirred under nitrogen and cooled to 5 °C. Diketene (Aldrich, stabilized with $CuSO_4$, 62 mL, 804 mmol) was added dropwise over 5 min, followed by trimethylsilyl chloride (103 mL, 806 mmol), added dropwise over 10 min (keeping the temperature below 10 °C). After stirring at 5 °C for a further 30 min, the reaction mixture was allowed to slowly warm to rt and stirred for a further 20 h. Water (1.5 L) was added and stirring was continued for a further 20 h. The reaction mixture was filtered and the collected solids were washed with water (500 mL), ether (200 mL), then dried in vacuo to give **6** (126 g, 93%) as a cream solid; ^{1}H NMR δ_H (300 MHz; DMSO-d_6) 11.23 (1H, s), 7.39 (1H, m), 7.04–7.13 (2H, m), 5.53 (1H, s), 5.06 (2H, s), 2.22 (3H, s); HRMS calcd for $C_{12}H_{10}F_2N_2O_2$ 253.0783 (M + H). Found: 253.0780 (M + H).
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stirred solution of bromoketone **9** (27 mg, 0.046 mmol) and 4-chlorothiobenzamide (10 mg, 0.05 mmol) in ethanol (1 mL) was heated at 80 °C for 2 h. The reaction mixture was cooled and solvent was removed in vacuo. The residue was redissolved in a mixture of dichloromethane (1 mL) and trifluoroacetic acid (1 mL) and stirred at rt for 1 h. The solvent was removed in vacuo and purification via preparative LC–MS afforded **11j** (15 mg, 48%) as a colorless solid; ^{1}H NMR δ_H (300 MHz; $CDCl_3$) 7.77–7.80 (2H, m), 7.35–7.41 (5H, m), 7.17–7.32 (4H, m), 6.87–6.93 (2H, m), 5.19 (2H, s), 4.52–4.61 (2H, m), 3.96 (1H, m), 2.21 (3H, s); HRMS calcd for $C_{29}H_{23}ClF_2N_4O_2S$ 565.1271 (M + H). Found: 565.1269 (M + H).

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20. Compound **13** was previously prepared by this group. Unpublished results.
21. The calculated log P values for 2-methylthiophene, 2-methylthiazol-4-yl and 2-aminothiazol-4-yl are approximately 2, 1 and 0.5, respectively. These calculated values were obtained using ACD/Labs LogP database, version 6.0 (2002), Advanced Chemistry Development Inc., Toronto, Ontario, Canada (http://www.acdlabs.com).
22. Based on a docking study using a GnRH homology model obtained from the crystal structure of b-rhodopsin, we speculate that the C-5 substituent (of the uracil core) sits close to the extracellular surface of the receptor between TM domains 4 and 5. Unpublished results.