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Efficient synthesis of bicyclic oxazolino- and thiazolino[3,2-*c*]pyrimidine-5,7-diones and its application to the synthesis of GnRH antagonists

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Abstract—Treatment of various 2-methyl oxazolines or thiazolines with chlorocarbonyl isocyanate gives the corresponding bicyclic oxazolino- or thiazolino[3,2-*c*]pyrimidin-5,7-dione derivatives in very good yield. This reaction has been applied to the rapid syntheses of human gonadotropin-releasing hormone (*h*GnRH) receptor antagonists for SAR study, resulting in **13e** with binding affinity in the low nanomolar range (4.5 nM).

Gonadotropin-releasing hormone (GnRH) is a decapeptide released from the hypothalamus.[1] It stimulates the GnRH receptor in the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn regulate gonadal steroid hormone production.[2] Down-regulation of the hypothalamic–pituitary–gonadal hormonal axis with peptidic GnRH agonists has been shown to alleviate disease conditions associated with endometriosis, uterine fibroids, breast, and prostate cancer.[3] The recent search for orally available, non-peptide GnRH antagonists has resulted in the disclosure of several classes of small molecules that strongly bind to, but do not activate, the human GnRH (*h*GnRH) receptor. These include the thieno[2,3-*d*]pyridin-2,4-diones,[4a] the 1*H*-quinolones,[4b] the 2-arylindoles,[4c] the aminopyrimidines,[4d] the arylpyrrolo[1,2-*a*]pyrimidones,[4e] the imidazolo[1,2-*a*]pyrimidones,[4f] and very recently the uracils such as **1a**[4g] and **1b**[4h] (Fig. 1).

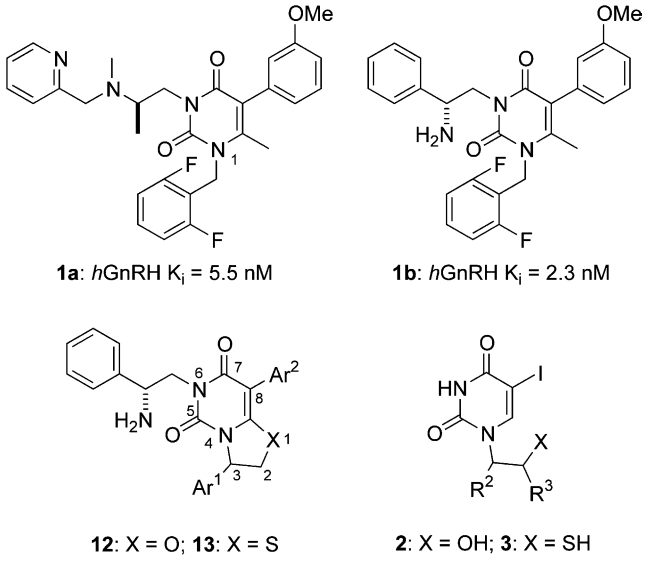

Figure 1.

The present work was initiated in an attempt to develop a bicyclic system that conformationally locks the 1-benzyl ring of compounds **1a**,**b**, because in the crystal structure of a closely related analog, the phenyl ring of this benzyl group is tilted away from the uracil plane.[5] A bicyclic system such as **12** or **13** may constrain the phenyl ring in order to emulate low-energy conformations of uracils **1**, which may result in more potent compounds. The cores of these bicylic systems could in theory be obtained by cyclization of the corresponding alcohol **2** and thiol **3** under basic conditions, a method used for furanosyluracil synthesis.[6] However, the availability of the starting material and the strongly basic reaction conditions required are limiting factors in these syntheses. A Bayer patent described the reaction of

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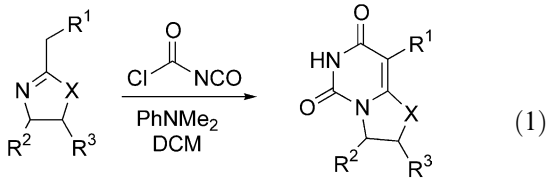
benzoxazoles and benzothiazoles with chlorocarbonyl isocyanate to give benzoxazolopyrimidinediones and benzothiazolopyrimidinediones.[7] We thought that this reaction would be ideally suited for the synthesis of the bicyclic oxazolidino- and thiazolidino[3,2-*c*]pyrimidin-5,7-dione systems **6** and **7** from the readily available oxazolines **4** and thiazolines **5** (Eq. 1). In addition, this straightforward chemistry would provide rapid access to analogs for SAR study.



4: X = O
5: X = S

6: X = O
7: X = S

(1)

The generality of this reaction was explored with a number of different commercially available[8] or synthesized[9,10] oxazoline and thiazoline substrates. Thus treatment of solutions of oxazolines **4** or thiazolines **5** in the presence of dimethylaniline with chlorocarbonyl isocyanate at 0 °C to room temperature gave the bicyclic products **6a**–**e** and **7a**–**e** (Table 1).[11] The reaction proved to be successful with a variety of oxazolines and thiazolines, giving simple, non-substituted products (e.g., **6a**, **7a**) to those incorporating two aromatic rings (**6e**, **7b**–**e**). The reactions worked equally well for oxazolines and thiazolines; the non-optimized yields ranged from 70% to 89%. Furthermore, the products were generally solids, and easily separated from the reaction mixtures.

Table 1. Cyclization reaction results

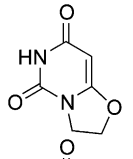
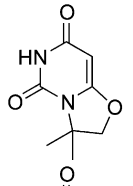
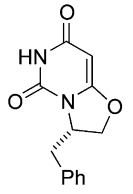
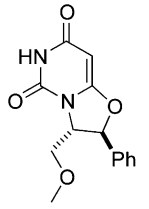
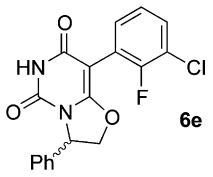
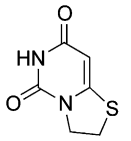
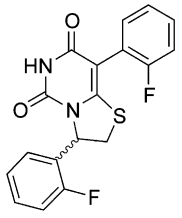
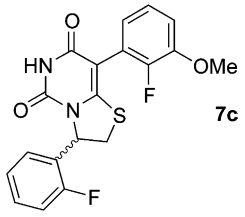
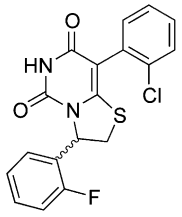
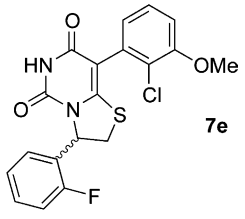
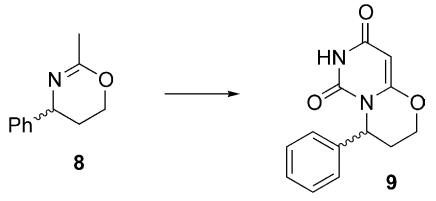
Product	Yield (%)
 **6a**	86
 **6b**	78
 **6c**	89
 **6d**	76

Table 1 (*continued*)

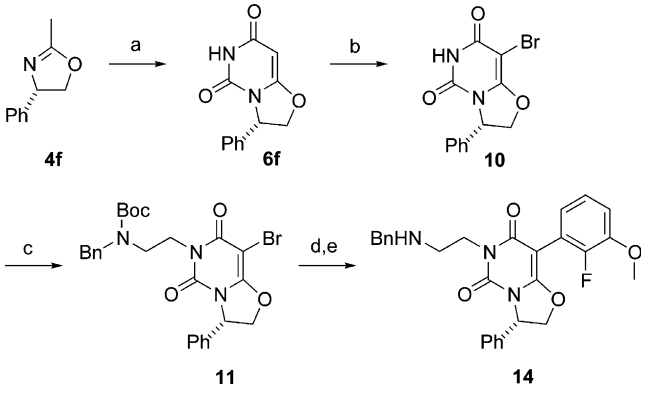
Product	Yield (%)
 **6e**	70
 **7a**	86
 **7b**	82
 **7c**	80
 **7d**	76
 **7e**	74

The scope of this reaction was further broadened by its application to the synthesis of the corresponding 6,6-ring system. Thus reaction of the dihydroxazine **8**[12] with chlorocarbonyl isocyanate in the presence of dimethylaniline under the same conditions gave the novel, bicyclic uracil derivative **9** in 78% yield (Eq. 2).

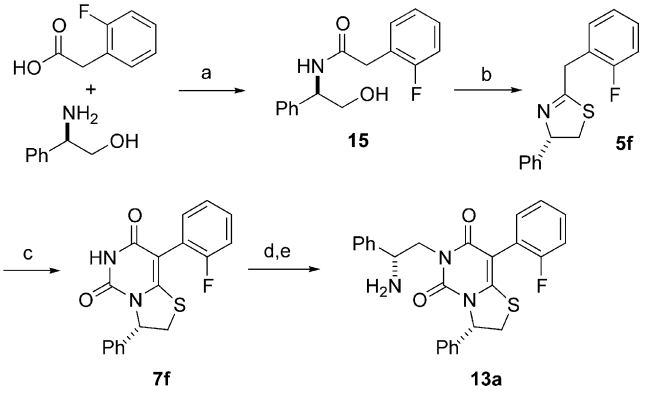


8 **9**

(2)



Scheme 1. Reagents and conditions: (a) ClC(O)NCO, $PhNMe_2$, DCM (81%); (b) NBS, THF (86%); (c) $BnN(Boc)CH_2CH_2OH$, Ph_3P, DEAD, THF (80%); (d) $[(2\text{-F},3\text{-OMe})Ph]B(OH)_2$, $Pd(Ph_3)_4$ (cat.), $Ba(OH)_2$ (aq), dioxane/C_6H_6/EtOH (10:9:1), Δ; (e) TFA, DCM (67%, two steps).



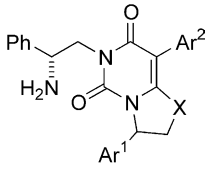
Scheme 2. Reagents and conditions: (a) HOBt, EDC, DCM (91%); (b) P_2S_5, DCM (91%); (c) ClC(O)NCO, $PhNMe_2$, DCM (79%); (d) *N*-Boc-(*R*)-phenylglycinol, Ph_3P, DEAD, THF; (e) TFA, DCM (70%, two steps).

The success of this reaction led to the development of efficient syntheses of small molecule GnRH antagonists. The first representative synthesis (Scheme 1) involves reaction of the known oxazoline **4f**, prepared by condensation of *R*-phenylglycinol with triethylorthoacetate,[12] with chlorocarbonyl isocyanate to give the oxazolinopyrimidinedione **6f** (81%). Subsequent bromination with NBS to give **10**, followed by Mitsunobu reaction with (*N*-Boc, *N*-benzyl)ethanolamine, yielded the 6-bromooxazolinopyrimidinedione derivative **11**. Finally, incorporation of the right (2-fluoro, 3-methoxy)phenyl ring by Suzuki coupling, and subsequent Boc deprotection gave the oxazolinopyrimidinedione derivative **14** in 67% yield (two steps). Because this synthesis ended with a Suzuki coupling, it was well suited to SAR study on the right side of the system.

The second representative synthesis (Scheme 2) begins with the coupling of (*R*)-phenylglycinol with 2-fluorophenylacetic acid under standard coupling conditions. The amide **15** thus obtained was then converted to the thiazoline **5f** in 91% yield.[9b] The key cyclization reaction in the presence of chlorocarbonyl isocyanate gave the thiazolinopyrimidinedione **7f** in 79% yield. Subsequent Mitsunobu reaction with *N*-Boc-(*R*)-phenylglycinol under standard conditions, followed by Boc deprotection, provided the amine **13a** in 70% yield. Since this synthesis ended with a Mitsunobu coupling (or alternatively, simple alkylation), it was ideally suited to SAR study on the left side of the system.

Binding affinities of an initial set of compounds were determined[13] and are summarized in Table 2. The set was modeled on analogs **1a**,**b** in hopes of achieving good binding affinities to the *h*GnRH receptor. Indeed, the first compound **14**, which has a benzylaminoethyl side chain similar to **1a**, displayed modest binding activity at 460 nM. In this series, however, the side chain derived from (*R*)-phenylglycinol (as in **1b**) gave better binding activity and was thus utilized in subsequent compounds. In addition, compounds with '*S*' chirality at C_3 of the bicyclic core were much more active; (*R*)-**14** and (*R*)-**13a** (not shown) had binding affinities in the high

Table 2. Binding affinities of compounds **12–14** to the *h*GnRH receptor[13]



12: X = O; **13**: X = S

Compound	C_3 chirality	Ar^1	Ar^2	K_i (nM)
14	*S*	Phenyl	(2-Fluoro, 3-methoxy)phenyl	460
12a	*RS*	Phenyl	2-Fluorophenyl	700
12b	*RS*	2-Fluorophenyl	2-Fluorophenyl	230
12c	*RS*	Phenyl	3-Methoxyphenyl	870
12d	*RS*	Phenyl	(2-Fluoro, 3-methoxy)phenyl	125
13a	*S*	Phenyl	2-Fluorophenyl	110
13b	*RS*	2-Fluorophenyl	2-Fluorophenyl	220
13c	*RS*	2-Fluorophenyl	(2-Fluoro, 3-methoxy)phenyl	40
13d	*RS*	2-Fluorophenyl	2-Chlorophenyl	93
13e	*RS*	2-Fluorophenyl	(2-Chloro, 3-methoxy)phenyl	4.5

micromolar range. Other compounds **12a**–**d** and **13b**–**e** were tested as mixtures of diastereomers.

In comparing the oxazolino[3,2-*c*]pyrimidin-5,7-dione cases **12a** and **12b**, incorporation of a 2-fluoro substituent on the bottom phenyl ring slightly increased activity to 230 nM. The 3-methoxyphenyl derivative **12c** showed modest activity (870 nM). However, incorporation of the 2-fluoro, 3-methoxyphenyl substitution pattern in **12d** resulted in good binding activity (125 nM).

The thiazolino[3,2-*c*]pyrimidin-5,7-diones **13** showed somewhat similar SAR patterns. The sulfur derivative **13b** (220 nM) was equipotent to oxo-derivative **12b**. Incorporation of the (2-fluoro, 3-methoxy)phenyl moiety in **13c** increased binding activity to 40 nM, an almost 6-fold increase. Interestingly, incorporation of the 2-chlorophenyl substituent (**13d**) also slightly improved binding affinity over the 2-fluorophenyl case. Moreover, the best substitution pattern in this series is the (2-chloro, 3-methoxy)phenyl of **13e**. This potent compound displayed a *h*GnRH binding affinity of 4.5 nM.

In summary, we have shown that reaction of substituted 2-methyl oxazolines or thiazolines with chlorocarbonyl isocyanate gives the oxazolino- or thiazolino[3,2-*c*]pyrimidin-5,7-dione derivatives in very good yield. This reaction has been applied to the rapid syntheses of substrates active against the *h*GnRH receptor. The first synthesis ends with a Suzuki coupling, making the synthesis ideally suited to the development of SAR on the right side of the molecule, while the second synthesis ends with a Mitsunobu coupling, rendering the synthesis well suited to development of SAR on the left side of the system. The best compound in the series displayed binding in the low nanomolar range with **13e** having a K_i of 4.5 nM. Further SAR studies of these systems will be reported in due course.

Acknowledgements

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7. Bayer Patent (Germany) DE 2126148; *Chem. Abstr*. **1972**, *78*, 11360.
8. The oxazolines **4a**, **4c**–**d** and thiazoline **5a** were purchased from Sigma-Aldrich. The oxazoline **4b** was purchased from Lancaster Synthesis.
9. (a) The oxazoline **4e** was synthesized according to known literature procedures, see: Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 2044; (b) The thiazolines **5b**–**f** were synthesized according to known literature procedures, see: Aitken, R. A.; Armstrong, D. P.; Galt, R. H. B.; Mesher, S. T. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2139.
10. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, LCMS, and elemental analysis or HRMS.
11. Representative procedure (see Scheme 1): To (*S*)-2-methyl-4-phenyl-4,5-dihydrooxazole (**4f**) (1.82 g, 11.3 mmol) and dry *N,N*-dimethylaniline (1.49 g, 12.3 mmol) in dry dichloromethane (8 mL) under N_2 at 0 °C was added dropwise chlorocarbonyl isocyanate (1.24 g, 11.8 mmol). The mixture was allowed to warm to room temperature and stirred for 14 h, during which time a thick white precipitate formed. The suspension was filtered, and the solid triturated with cold dichloromethane (3 × 2 mL) to give 3-phenyl-2,3-dihydroxazolo[3,2-*c*]pyrimidine-5,7-(6*H*)-dione (**6f**) as a white amorphous powder (2.11 g, 81%). ^{1}H NMR (DMSO-D_6, 500 MHz): δ 10.95 (s, 1H); 7.42–7.39 (m, 2H); 7.37–7.33 (m, 1H); 7.28–7.26 (m, 2H); 5.57 (dd, J = 3.7, 8.3 Hz, 1H), 5.11 (s, 1H); 5.00 (dd, J = 8.8, 8.8 Hz, 1H); 4.54 (dd, J = 3.4, 8.8 Hz, 1H). ^{13}C

NMR (DMSO-D_6, 500 MHz): δ 164.9, 162.8, 147.4, 138.3, 128.9, 128.4, 126.0, 77.2, 75.5, 57.4. HRMS (EI) *m/e* $(M)^+$ calcd for $C_{12}H_{10}N_2O_3$: 230.0691, found 230.0686.

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13. All final compounds were evaluated for their ability to inhibit des-Gly10[125I-Tyr5, DLeu6, NMeLeu7, Pro9-NEt]-GnRH radioligand binding to the cloned hGnRH receptor stably expressed in HEK293 cells, using a 96-well filtration assay format; see: Perrin, M. H.; Haas, Y.; Rivier, J. E.; Vale, W. W. *Mol Pharmacol.* **1983**, *23*, 44, Data are the average of two or more independent experiments.