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THIAZOLO[4,5-d]PYRIMIDINE THIONES AND -ONES AS CORTICOTROPIN-RELEASING HORMONE (CRH-R1) RECEPTOR ANTAGONISTS

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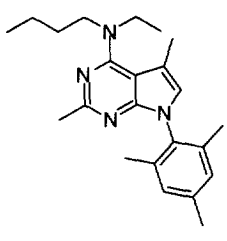
Abstract: A series of thiazolo[4,5-d]pyrimidine thiones and -ones was prepared and discovered to have good binding affintity to the CRH-R1 receptor, thus showing promise as a new class of potential anxiolytics and/or antidepressants.

The development of new pharmacotherapies for the treatment of anxiety and depression remains an area of active research.[1,2] In particular, the design of small molecule, nonpeptide antagonists for the corticotropin-releasing hormone (CRH) R1 receptor may afford new treatment options.[3] CRH, a 41-amino acid neuro-transmitter, plays an integral role in regulating mammalian stress response via action upon the hypothalamic-pituitary adrenal (HPA) axis,[4] and the finding that CRH may be hypersecreted in depressed patients lends support to the design of antagonists of CRH receptors.[3, 5]

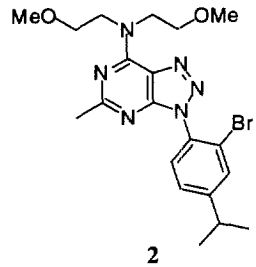
Several accounts of small molecule antagonists have appeared in the literature, including CP154526-1,[6] triazolopyrimidine **2**,[7] and many others[8–11] (Figure 1). In addition, preclinical pharmacology has been reported for one of these agents, CP154526-1.[12] Recent efforts in our laboratory have focused on the evaluation of diverse heterocycles that may potentially serve as CRH-R1 antagonists.[13] In this communication we detail the synthesis and preliminary structure–activity studies for a novel series of thiazolo[4,5-d]pyrimidine thiones and -ones (**6** and **7**) which show good affinity for the CRH-R1 receptor *in vitro*.[14]

Thiazolo[4,5-d]pyrimidines are known from the literature to possess antimicrobial activity[15] and CNS depressant activity.[16] General synthetic methods employed in the synthesis of thiazolo[4,5-d]pyrimidines are

Figure 1



CP154526-1



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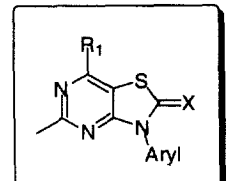

6, X = S
7, X = O

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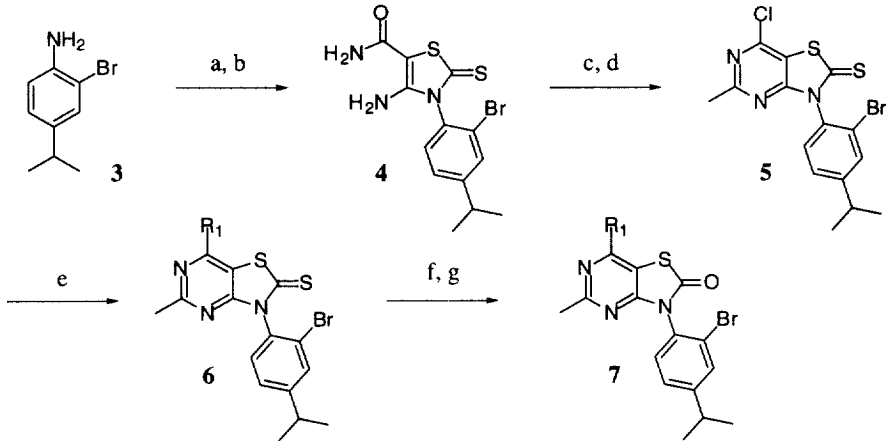
described in Scheme 1. Commercially available aniline **3** (or 2,4,6-trimethylaniline) was converted to the isothiocyanate and treated with cyanoacetamide and elemental sulfur as described by Gewald[17] to afford thiazolothione **4**. Pyrimidine formation with acetic anhydride followed by chlorination provided the desired core **5** in excellent yield.[18] Addition of amines cleanly generated the CRH-R1 targets **6** which could further be treated with dimethyl sulfate and hydrolyzed to yield the thiazolones **7**.[19] Yields for thiazolone formation were variable, and were consistently low when R_1 was substituted with alkoxy groups, likely due to overalkylation from dimethylsulfate.

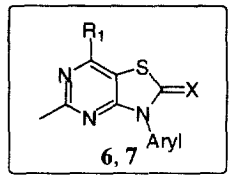
Scheme 1



Scheme 1: (a) thiophosgene, Na_2CO_3, DMF, 0 °C, 20 min; (b) cyanoacetamide, sulfur, Et_3N, DMF, rt, 2 h, 63% (from aniline); (c) acetic anhydride, reflux, 2.5 h, 97%; (d) $POCl_3$, reflux, 3 h, 85-95%; (e) amine (R_1), acetone, reflux, 2–5h, 85–98%; (f) $SO_2(OMe)_2$, 130 °C, 1 h; (g) H_2O, reflux, 2 h, 10–75% (from **6**).

Table 1 details the preliminary structure–activity relationship studies for derivatives of **6** and **7**. New compounds were assayed against transfected human CRH-R1 receptors expressed in HEK 293E cells.[19] 2-Bromo-4-isopropylphenyl was selected for aryl substitution from SAR work in previous series.[7,13] Introduction of a morpholine group provided **6a**, which showed only modest affinity for the CRH-R1 receptor. Binding affinity improved an order of magnitude, however, when noncyclic dialkyl amines were introduced to provide **6b** and **6c** (K_i = 4.1 nM and 12.6 nM, respectively). Optimal activity was observed with ethyl and n-propyl chain lengths; longer and bulkier alkyl chains provided the less potent analogs **6d** and **6e**. Not surprising from these preliminary studies was the excellent activity observed for dialkoxy substituted analog **6f** (K_i = 6.6 nM), though these results are in sharp contrast to the SAR observed for the structurally related purin-8-one series of CRH-R1 antagonists reported from our lab.[13] The corresponding thiazolones **7a**, **7b**, and **7c** (Table 1) also showed good binding affinity for the CRH-R1 receptor and were generally equipotent with their thiazolothione precursors. A comparison between 2-bromo-4-isopropylphenyl analogs and a second series of target compounds prepared from 2,4,6-trimethylaniline is also shown in Table 1. The thiocarbonyl analogs **6g-i** as well as the carbonyl derivatives

Table 1 Structure–Activity Relationships for Thiazolo[4,5-d]pyrimidine Thiones and -Ones.



6, 7

Compd	R_1	X	K_i (nM)[a]	Compd	R_1	X	K_i (nM)[a]
Aryl = 2-bromo-4-isopropylphenyl				Aryl = 2,4,6-trimethylphenyl			
6a	morpholino	S	122	**6g**	$N(Et)_2$	S	9.2 ± 5.3
				7d	$N(Et)_2$	O	14.5 ± 5.4
6b	$N(Et)_2$	S	4.1 ± 0.3				
7a	$N(Et)_2$	O	9.4 ± 2.1	**6h**	$N(n\text{-}Pr)CH_2$cyclo-Pr	S	13.1 ± 2.0
				7e	$N(n\text{-}Pr)CH_2$cyclo-Pr	O	16.2 ± 0.3
6c	$N(n\text{-}Pr)CH_2$cyclo-Pr	S	12.6 ± 6.4				
7b	$N(n\text{-}Pr)CH_2$cyclo-Pr	O	4.1 ± 3.4	**6i**	$N(CH_2CH_2OMe)_2$	S	8.6 ± 2.9
				7f	$N(CH_2CH_2OMe)_2$	O	5.0 ± 1.8
6d	N(Et)n-Bu	S	23.9 ± 6.2				
6e	$N(sec\text{-}Bu)_2$	S	45.4 ± 31.4				
6f	$N(CH_2CH_2OMe)_2$	S	6.6 ± 2.5				
7c	$N(CH_2CH_2OMe)_2$	O	14.5 ± 8.6				

a) Binding affinity was measured at transfected human CRH R1 receptors expressed in HEK 293E cells using ^{125}I-tyr-oCRH as the displaced radioligand.[19] Values are the average of $n \geq 2$ when $Ki < 50$ nM.

7d–f possessed good CRH R1 binding affinity and afforded activity similiar to the disubstituted phenyl series. The dialkoxy analog **7f** (K_i = 5.0 nM) was the most potent member of this series.

Efforts to further characterize the properties of the title compounds included a determination of the extent of protein binding.[20] An *in vitro* competition experiment was performed with binding to the CRH-R1 receptor challenged by the presence of human serum albumin (HSA, 4.5%) and α_1-acid glycoprotein (AAG, 0.1%). The resultant IC_{50} was divided by the control IC_{50} to provide a fold shift in the IC_{50}s; the larger the fold shift, the greater the relative indication of small molecule bound by plasma protein. The measured fold shifts for **6b**, **6f**, and **7a** were 9.8, 26.2, and 29.3 respectively, indicating thiazolothione **6b** was least bound to HSA and AAG.

In summary, we have synthesized a series of thiazolo[4,5-d]pyrimidine thiones and -ones that show good affinity for the CRH-R1 receptor *in vitro* and that may represent a new class of anxiolytics and/or antidepressants. In addition to work focused on defining the physiochemical properties of this new series (i.e., protein binding, lipophilicity, solubility), future studies to be reported in due course will continue to elucidate the SAR of alkyl vs alkoxy amine substitution on heterocyclic CRH-R1 receptor antagonists.

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