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Heterocyclic Analogs of the Benzolactam Nucleus of the Non-Peptidic Growth Hormone Secretagogue L-692,429

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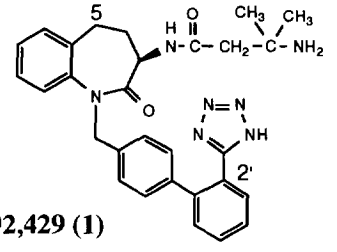
Abstract: A series of analogs of the non-peptidic benzolactam growth hormone secretagogue L-692,429 was prepared with heteroatom substitutions at the 5-position of the benzolactam ring. Replacement of the 5-position with sulfur or oxygen resulted in secretagogues of approximate equal potency to L-692,429 in the rat pituitary cell assay. Substitution of the 5-position with a carbonyl group or hydroxyl group and replacement of the benzolactam with the 1,4-benzodiazapin-2-one ring system gave analogs of greatly diminished *in vitro* activity.

L-692,429 (**1**) is a novel non-peptidic growth hormone secretagogue which has been shown to be clinically effective for the release of growth hormone in humans.[1,2] The benzolactam nucleus appears to be a critical template from which are appended the two important pharmacophores: the biphenyl tetrazole moiety and the dimethyl-β-alanine sidechain.[1b] We recently reported the structure-activity relationships of the 2'-position of the biphenyl moiety[3] as well as those of the amino acid sidechain[4] of L-692,429. In this Letter, we present the structure-activity relationships of the 5-position of the benzolactam nucleus of L-692,429 by replacement of that template with several different heterocyclic ring systems.



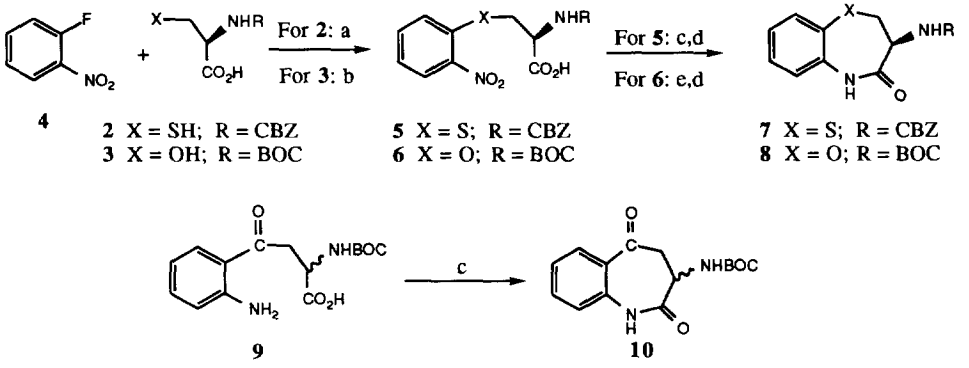
L-692,429 (1)

Chemistry

The heterocyclic templates were prepared according to known procedures as described in SCHEMES I, II, III and IV.[5] The 5-thia and 5-oxa analogs of L-692,429 were prepared with the desired configuration from the corresponding *N*-protected D-amino acids cysteine (**2**) and serine (**3**) as shown in Scheme I. Reaction of the protected amino acids with 2-fluoro-1-nitrobenzene (**4**) under basic conditions gave the S-phenyl cysteine intermediate **5** and the O-phenyl serine intermediate **6** in good yield. Zinc reduction of the nitro group of compound **5** and cyclization of the resulting aminophenyl cysteine intermediate with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDAC) completed the CBZ-protected 3(S)-aminobenzothiazepinone ring system **7**.[6] Similarly, hydrogenation of intermediate **6** and EDAC cyclization gave the BOC-protected

3(R)-aminobenzoxazepinone ring system **8**.[7] *N*-BOC-D,L-Kynurenine (**9**) was the starting material for the benzazepine-3,5-dione ring system. Cyclization of compound **9** with EDAC gave the known racemic *N*-BOC-5-oxobenzolactam[8] (**10**), albeit in only 18% yield .

SCHEME I

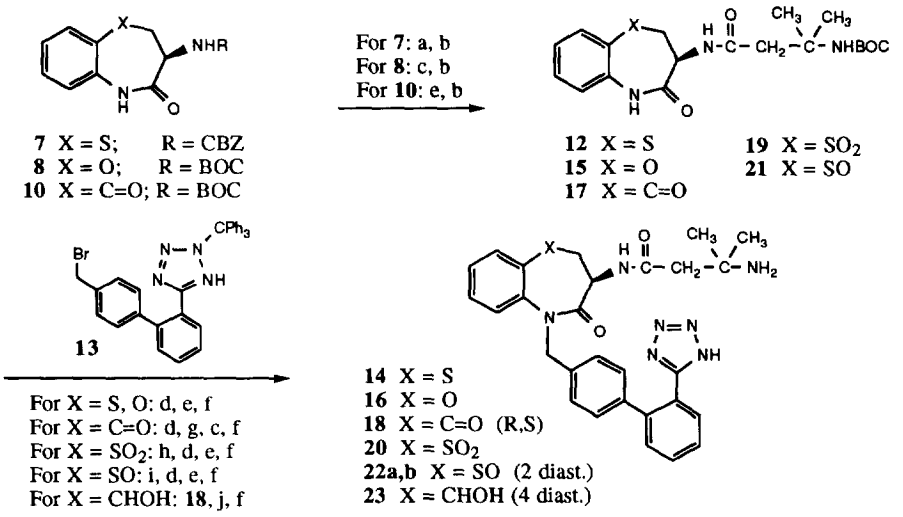


Reagents and conditions: (a) $NaHCO_3$, aq. EtOH, reflux, 3hr; (b) NaH, DMF, 0°-RT, 4hr; (c) Zn, NH_4Cl, MeOH; (d) EDAC, DMF, RT; (e) H_2/Pd-C, MeOH.

The conversion of these heterocyclic templates to the secretagogue targets was completed by chemistry described previously for L-692,429 (SCHEME II).[1b] Deprotection of the CBZ-group of thia intermediate **7** with HBr/HOAc, then coupling with *N*-BOC-3,3-dimethyl-β-alanine (**11**) using the BOP-reagent, gave amide **12** in excellent yield (92%). Treatment of intermediate **12** with sodium hydride followed by addition of biphenyltetrazole bromide **13** resulted in alkylation of the benzothiazepinone nitrogen. Removal of the protecting groups with 9N HCl in methanol followed by reverse phase medium pressure column chromatography afforded the 5-thia analog of L-692,429, **14**. Similarly, the benzoxazepinone intermediate **8** was deprotected with trifluoroacetic acid (TFA) and coupled to protected amino acid **11** to give amide **15**. Alkylation of intermediate **15** with biphenyl bromide **13** and deprotection gave the 5-oxa analog **16**. Similarly 5-oxobenzolactam intermediate **10** was converted to amide **17**, which upon alkylation and two-step deprotection sequence (hydrogenation followed by TFA), afforded the racemic 5-oxo analog **18** (only R-form shown).

Several analogs of 5-thia compound **14** and 5-oxo-compound **18** with differing oxidation states were prepared from key intermediates in SCHEME II. Oxidation of the benzothiazepinone sulfur of intermediate **12** with 2 equivalents of 3-chloroperbenzoic acid gave sulfone **19** which was smoothly converted to sulfone target compound **20** by the alkylation/deprotection sequence. Alternatively, oxidation of **12** with sodium periodate afforded two diastereomeric sulfoxides **21**, which were separable by silica gel chromatography (less polar sulfoxide assigned **a** in final product). Conversion to the target sulfoxides as previously described gave analogs **22a,b**. Treatment of 5-oxo analog **18** with sodium borohydride in aqueous methanol followed by reverse phase MPLC gave the 5-hydroxy benzolactam product **23** (as a racemic mixture of two diastereomers).

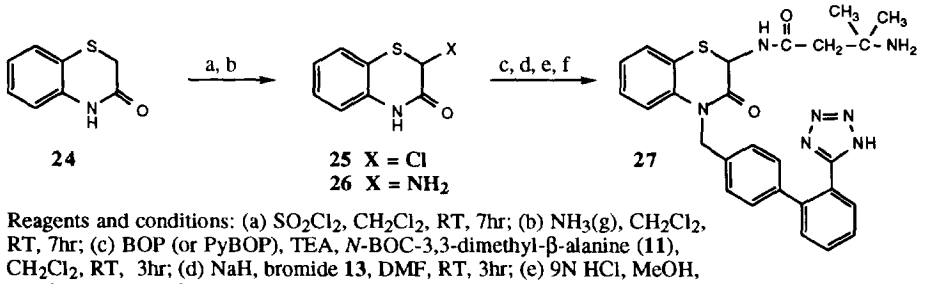
SCHEME II



Reagents and conditions: (a) HBr-HOAc, 0°, 1hr; (b) BOP (or PyBOP), TEA, *N*-BOC-3,3-dimethyl-β-alanine (**11**), CH_2Cl_2, RT, 3hr; (c) TFA, anisole, CH_2Cl_2; (d) NaH, bromide **13**, DMF, RT, 3hr; (e) 9N HCl, MeOH, RT, 6-24hr; (f) RPLC on C-8, MeOH/0.1% Aq. TFA (55:45); (g) H_2 balloon/ $Pd(OH)_2$, RT, 16hr; (h) 80% MCPBA, $NaHCO_3$, CH_2Cl_2, RT, 3hr; (i) $NaIO_4$, MeOH/H_2O (5:1), RT, 48hr; (j) $NaBH_4$, MeOH/H_2O (4:1). RT, 1 hr.

The analog of L-692,429 containing a benzothiazinone template (6-membered thia analog) in place of the benzolactam moiety was prepared as shown in SCHEME III. The benzothiazinone **24** was converted to the known 3-chloro derivative[9] **25** by treatment with sulfuryl chloride. Reaction of the crude chloro compound with ammonia gas afforded 3-aminobenzothiazinone **26**. Conversion to the target benzothiazinone analog **27** proceeded smoothly *via* the standard route of amide formation with acid **11**, alkylation with bromide **13**, deprotection and purification.

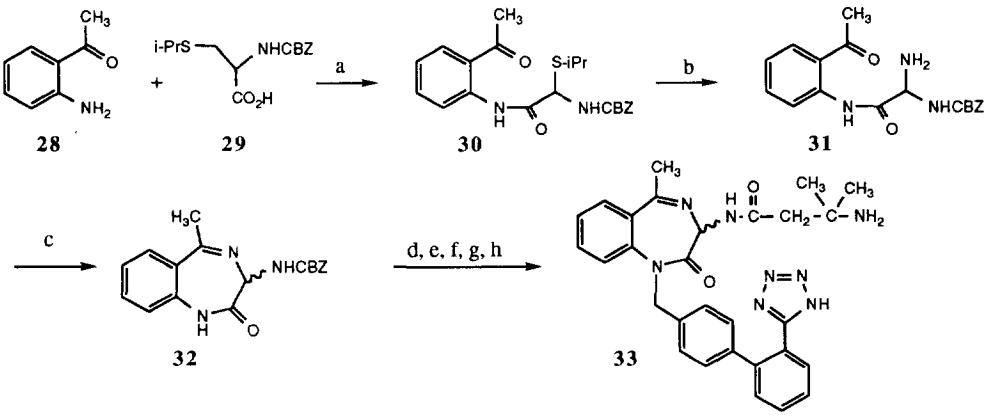
SCHEME III



Reagents and conditions: (a) SO_2Cl_2, CH_2Cl_2, RT, 7hr; (b) NH_3(g), CH_2Cl_2, RT, 7hr; (c) BOP (or PyBOP), TEA, *N*-BOC-3,3-dimethyl-β-alanine (**11**), CH_2Cl_2, RT, 3hr; (d) NaH, bromide **13**, DMF, RT, 3hr; (e) 9N HCl, MeOH, RT, 24hr; (f) RPLC on C-8, MeOH/0.1% Aq. TFA (55:45).

The analog of L-692,429 containing a 1,4-benzodiazepinone template in place of the benzolactam ring was prepared as shown in SCHEME IV. Coupling of 2-aminoacetophenone (**28**) with the mixed anhydride of *N*-CBZ-2-isopropylthioglycine[10] (**29**) gave glycine amide derivative **30**. Treatment with ammmonia and mercuric chloride afforded the 2-aminoglycine amide **31**, which upon heating in acetic acid with ammonium acetate cyclized to the *N*-CBZ-3-aminobenzo-1,4-diazepin-2-one **32**. This intermediate was then converted to analog **33** by the addition of the two key sidechains and appropriate deprotection.

SCHEME IV



Reagents and conditions: (a) i-butyl chloroformate, *N*-methylmorpholine, CH_2Cl_2, 0°-RT,16hr; (b) NH_3(g), $HgCl_2$, THF, 0°-RT, 3hr; (c) NH_4OAc, HOAc, 55°, 3hr; (d) HCO_2H, Pd-C, MeOH; (e) BOP, TEA, *N*-BOC-3,3-dimethyl-β-alanine (**11**), CH_2Cl_2, RT, 3hr; (f) NaH, bromide **13**, DMF, RT, 3hr; (g) HBr-HOAc, 0°, 1hr; (h) RPLC on C-8, MeOH/0.1% Aq. TFA (55:45);

Results and Discussion

Growth hormone release *in vitro* was measured in rat pituitary cells as previously described.[1b,11] Table 1 displays data for the seven-membered ring series of heterocyclic analogs of L-692,429. Replacement of the 5-methylene unit of L-692,429 with either a sulfur or oxygen atom leads to essentially equipotent compounds *in vitro*. This shows a tolerance of a slightly larger ring size and increased lipophilicity in the case of the sulfur analog **14**, as well as, tolerance for the more polar oxygen atom in compound **16**. However, substitution of the 5-position with a carbonyl group, as in racemic analog **18**, leads to a greater than 20-fold decrease in potency in the rat pituitary cell assay (as compared to racemic L-692,429, **35** Table 2). This intolerance for substitution at the 5-position of the heterocyclic ring is also observed for sulfone analog **20**, sulfoxide analogs **22a,b** and 5-hydroxy analogs **23**. Therefore, substitution of the 5-methylene unit of L-692,429 with heteroatoms is tolerated in this series of secretagogues, while addition of polar substituents at the 5-position of the seven-membered ring leads to a large decrease in GH releasing activity. However, steric and conformational factors may also be contributing to this decrease in activity.

Table 2 shows the GH releasing activity of several other heterocyclic templates. The racemic benzothiazinone analog **27** was 4-fold less potent than the racemic analog of L-692,429, **35**.[1b] Comparison to the 6-membered

ring lactam analog **34** (2μM)[1b] demonstrates the trend that increasing the ring size from 6 to 7 is beneficial to GH releasing activity with the sulfur analog **27** possessing a ring of intermediate size as compared to carbon analogs **34** and **35**. The 1,4-benzodiazepin-3-one analog **33** was inactive in the GH release assay which is in contrast to the successful use of the benzolactam ring as a replacement for the 1,4-benzodiazepinone system in a series of CCK receptor antagonists.[12]

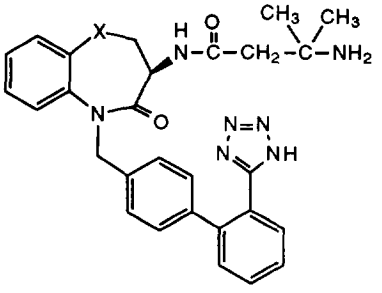


Table 1

Compound	X	$ED_{50}(\mu M)^a$
1	CH_2	0.06
14	S	0.10
16	O	0.12
18	CO[b]	2.7
20	SO_2	1
22a	SO[c]	4
22b	SO[d]	3
23	CHOH[e]	4

[a]Rat Pituitary Cell Assay [b]Racemic [c]Diastereomer 1 (less polar) [d]Diastereomer 2 (more polar) [e]Racemic mixture of diastereomers

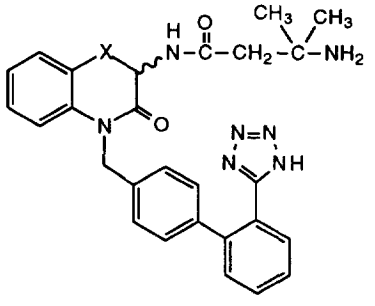


Table 2

Compound	X	$ED_{50}(\mu M)^a$
27	S	0.50
34	CH_2	2.0
35	CH_2CH_2	0.12
33	H_3C, $C=N$	inactive[b]

[a]Rat Pituitary Cell Assay [b]20μg/mL

Summary

A series of analogs of L-692,429 containing a variety of heterocyclic ring systems was prepared in order to explore the structure-activity relationships of the 5-position of the benzolactam template of the non-peptidic growth hormone secretagogue L-692,429. Replacement of the 5-methylene unit of benzolactam ring of L-692,429 with either a sulfur or oxygen atom leads to secretagogues with approximate equal potency in the GH release assay. Addition of substituents to the 5-position or heteroatom substitution at the 4-position leads to a

large decrease in secretagogue activity. Further studies on the structure-activity relationships of this class of growth hormone secretagogues will be disclosed later.

Acknowledgment

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