Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 11, pp. 1265-1270, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00213-2

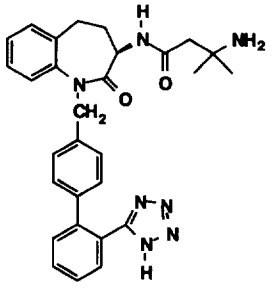
SYNTHESIS AND BIOLOGICAL ACTIVITIES OF CAMPHOR-BASED NON-PEPTIDE GROWTH HORMONE SECRETAGOGUES

Ravi P. Nargund,*[,†] Khaled H. Barakat,[†] Kang Cheng,[§] Wanda W.-S. Chan,[§] Bridget R. Butler,[§] Roy G. Smith,[§] and Arthur A. Patchett[†]

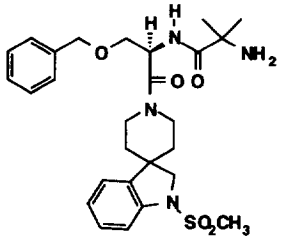
[†]*Departments of Medicinal Chemistry and Biochemistry and* [§]*Physiology*
Merck Research Laboratories, P. O. Box 2000, Rahway, NJ 07065.

Abstract: The synthesis and growth hormone (GH) releasing activities of a novel series of camphor-based non-peptide GH secretagogues is presented. Use of the (R)-nipecotic acid amino side-chain and N-terminal derivatization of it with an (R)-(2-hydroxy)propyl group provided a potent secretagogue **18** (EC_{50} = 90 nM). An *o*-tolyl piperazine was identified as a good replacement for the spiroindanyl piperidine.

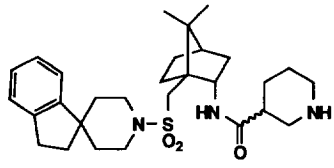
Since the discovery of the peptidyl growth hormone (GH) secretagogue GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2) **1** by Bowers and Momany[1] in the early 1980's considerable progress has been made towards identifying small molecules that mimic the mechanism of action and in vivo properties of **1**. Examples include the non-peptide **2** (L-692,429)[2a,b] and the recently disclosed orally active peptidomimetic **3** (MK-0677).[3] In this paper we present the synthesis and biological activities of a series of camphor-based GH secretagogues that evolved from structure–activity relationship studies that were carried out on a screening lead L-368,112. The discovery of this class of secretagogues formed the basis for utilizing the spiroindanyl piperidine "privileged structure" of **4** in a derivatization project from which a structurally distinct lead was identified and modifications of it culminated in the discovery of our clinical candidate MK-0677.[3]



2 (L-692,429)



3 (MK-0677)



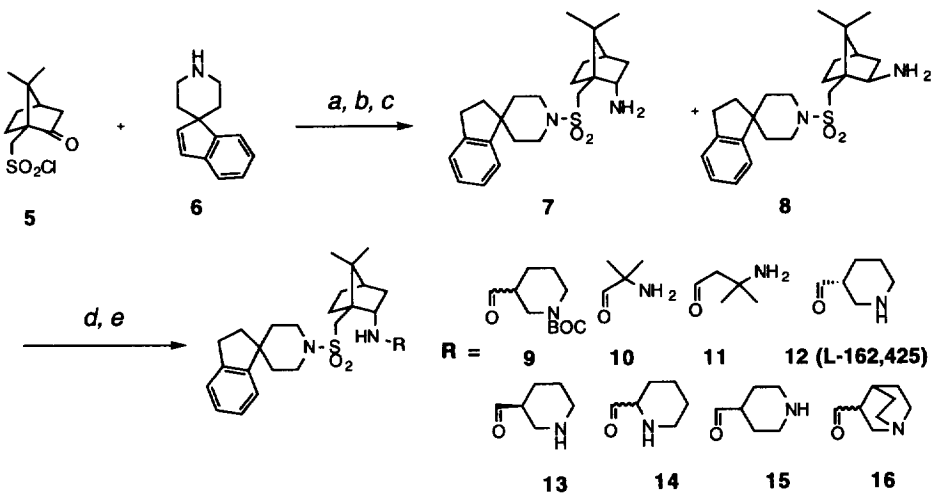
4 (L-368,112)

Chemistry

The camphor compounds were prepared according to known procedures as described in Schemes 1, 2, and 3. Camphor sulfonamides of formula **9–16** were prepared from (S)-(+)-camphorsulfonyl chloride **5** as shown in Scheme 1. Reaction of **5** with spiroindenylpiperidine hydrochloride **6**[4] in the presence of triethylamine, followed by conversion of the camphor ketone to its oxime derivative and reduction of it with freshly generated Raney nickel in ethanol according to the method of Evans et al.[5] gave a 4:1 mixture of the

endo and *exo* amines **7** and **8**. Their structure assignment was made based on chemical shift perturbation of one camphor methyl substituent by the *exo*, but not the *endo* amino group. Compounds **10–15** were prepared from amine **7** by coupling it with N-*t*-BOC protected amino acids using standard peptide-type coupling protocols and then removing the BOC group with strong acid (TFA in dichloromethane) to give compounds **10–15** as their trifluoroacetic acid salts in excellent yield. The N-*t*-BOC dimethyl β-alanine that was used in the synthesis of **11** was made according to the method of Schoen et al.[2b] (R) and (S) N-*t*-BOC nipecotic acids were synthesized by a three-step sequence starting with the resolution of (RS)-ethyl nipecotate, protection of the piperidine as its BOC derivative and subsequent hydrolysis of the ester with lithium hydroxide in THF-water. Compound **16** was prepared by coupling **7** with (RS)-quinuclidine 3-carboxylic acid.

SCHEME 1

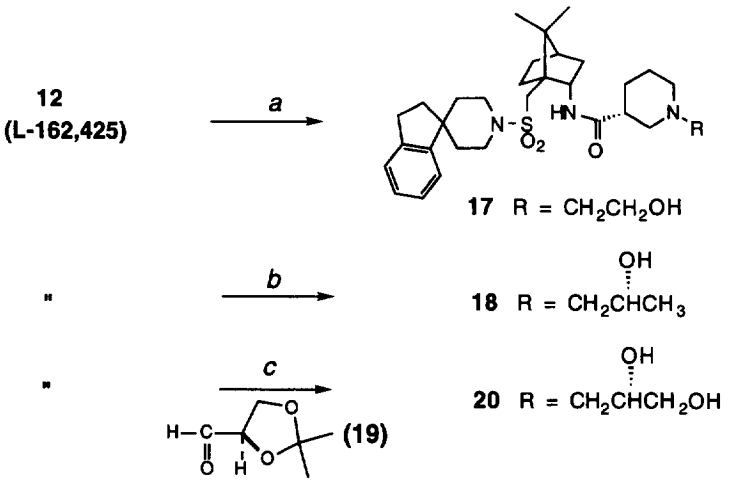


Reagents and conditions: (*a*) Et_3N, CH_2Cl_2; (*b*) $NH_2OH.HCl$, Py, 12 h; (*c*) Raney nickel, EtOH, H_2; (*d*) N-BOC protected amino acid, EDC, HOBT, CH_2Cl_2, 18 h; (*e*) TFA, CH_2Cl_2, 30 min.

As shown in Scheme 2, compound **17** in which the N-terminal amino acid was derivatized by incorporation of an hydroxyethyl substituent was prepared from **4** by first alkylating the piperidine with 2-*t*-butyldimethylsilyloxyethyl bromide and then removing the TBDMS group under acidic conditions. Reaction of **12** with (S)-propylene oxide (neat) containing a trace of triethylamine and neutral alumina gave **18** in good yield. Compound **20** was prepared by carrying out a reductive amination of **12** with D-glyceraldehyde acetonide[6] followed by removal of the dimethylacetal protecting group with aqueous TFA.

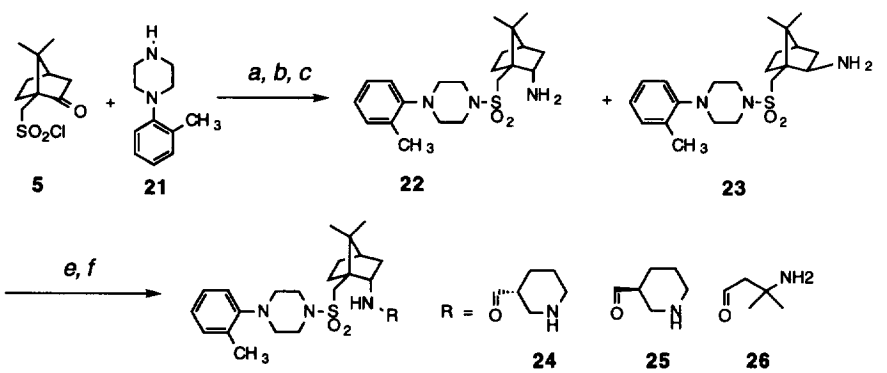
o-Tolyl piperazine-based GH secretagogues **24–26** were prepared from *endo* amine **22**. Following the method of Williams et al.[8] sulfonylation of *o*-tolyl piperazine **21** with (S)-camphor sulfonyl chloride **5** followed by transformation of the camphor ketone to its oxime and hydrogenation of it with freshly prepared Raney nickel Raney nickel gave a 3:1 mixture of **22** together with its *exo* isomer **23**. Elaboration of **22** to tolyl piperazine-based GH secretagogues **24–26** was carried out by taking advantage of chemistry that was employed for the synthesis of **10–15** (see Scheme 1).

SCHEME 2



Reactions and conditions: (*a*) $BrCH_2CH_2OTBDMS$, K_2CO_3, DMF, 50 °C, 18 h; (*b*) (S)-propylene oxide, Et_3N, neutral alumina,18 h; (*c*) **19**, $NaCNBH_3$, MeOH, NaOAc, 18 h; 50% aq.TFA, 18 h.

SCHEME 3

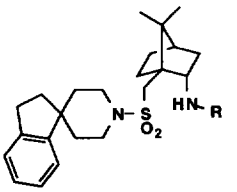


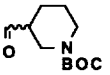
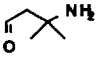
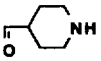
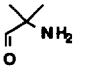
Reagents and conditions: (*a*) Et_3N, CH_2Cl_2; (*b*) $NH_2OH.HCl$, Py, 12 h; (*c*) Raney nickel, EtOH; (*d*) N-*t*-BOC protected amino acid, EDC, HOBT, CH_2Cl_2, 18 h, rt; (*e*) TFA, CH_2Cl_2, 30 min.

Results and Discussion

L-368,112, an (S)-(+)-camphorsulfonamide, was identified as a weakly active GH secretagogue from the screening of compounds from receptor projects in the rat pituitary cell GH release assay.[9] Table I highlights the potencies of compounds that were synthesized to study the SAR of the amino side-chain. Blocking the basic amine as depicted in **9** led to a considerable loss of intrinsic activity demonstrating that a basic amine was needed for GH secretion. This finding is consistent with the SAR of both peptidyl and peptidomimetic secretagogues.[1,2,3] We reasoned that the piperidine of L-368,112 was possibly binding in the same site as the N-terminus of the dimethyl β-alanine of L-692,429. Therefore, compounds **10** and **11** bearing the amino isobutyric acid and dimethyl β-alanine side chains were prepared and evaluated in the in vitro GH release assay.

TABLE I



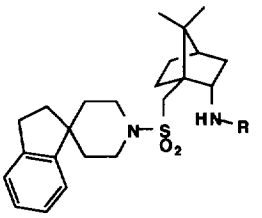
Compound	R	EC_{50} (μM)[a]	Compound	R	EC_{50} (μM)[a]
4 (L-368,112)		0.30	13		> 1
9		> 25	14		> 10
10		> 10	15		9.5
11		> 10	16		> 10
12 (L-162,425)		0.14			

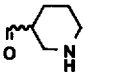
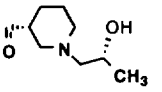
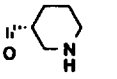
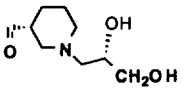
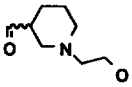
[a]Intrinsic GH secretory potency in the rat pituitary cell assay.[9] EC_{50} for half maximal release of GH is normalized for L-692,429 at 60 nM.

Unfortunately, these compounds were only weakly active. The individual diastereomers of L-368,112 were prepared and evaluated for their GH releasing ability. It was found that the camphor sulfonamide bearing the (R)-nipecotic acid side chain **12** (L-162,425) was considerably more potent than its (S)-nipecotic acid counterpart **13**. Shifting piperidine nitrogen to either the 2- or the 4-position of the piperidine (compounds **14** and **15**) led to a complete loss of GH secretory activity.

In their studies on benzolactam GH secretagogues Schoen et al.[7a] and Ok et al.[7b] have reported that the intrinsic activity of L-692,429 can be increased by nearly 20-fold by appending either a (R)-(2-hydroxy)propyl or a 2(R)-(dihydroxy)propyl unit on the dimethyl β-alanine amino side-chain. Our results with derivatization of the piperidine of **12** are shown in Table II. In the camphor series incorporation of only the (2R)-hydroxypropyl side chain (compound **18**) was found to provide a modest increase in the intrinsic activity. The activity of **18** (EC_{50} = 90 nM) is greater than the lead compound L-368,112 (EC_{50} = 300 nM) and it approaches that of the benzolactam L-692,429 (EC_{50} = 60 nM).

TABLE II

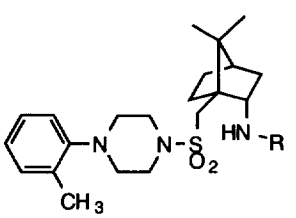


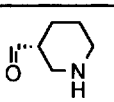
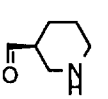
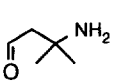
Compound	R	EC_{50} (μM)[a]	Compound	R	EC_{50} (μM)[a]
4 (L-368,112)		0.30	18		0.09
12 (L-162,425)		0.14	20		0.80
17 (R,S)		0.30			

[a]Intrinsic GH secretory potency in the rat pituitary cell assay.[9] EC_{50} for half maximal release of GH is normalized for L-692,429 at 60 nM.

In the oxytocin antagonist field an *o*-tolyl piperazine group has been found to be an excellent replacement for the spiroindanyl piperidine. Williams et al.[8] have reasoned that the *o*-tolyl methyl substituent orients the phenyl group orthogonal to the plane of the piperazine and thereby achieves the shape of a spiroindanylpiperidine. The activities of *o*-tolyl piperazine-based GH secretagogues are presented in Table III. Indeed, the *o*-tolyl piperazine group was found to be a satisfactory replacement for the spiroindanyl piperidine of **11**. The intrinsic potency of **24** is comparable to the activity of the spiroindane compound **12**. The SAR studies on amino side-chains indicated that, like the spiroindane secretagogues, the (R)-nipecotic acid amino side-chain was needed for GH releasing activity.

TABLE III



Compound	R	EC_{50} (μM)[a]
24		0.135
25		> 5
26		>10

[a]Intrinsic GH secretory potency in the rat pituitary cell assay.[9] EC_{50} for half maximal release of GH is normalized for L-692,429 at 60 nM.

Summary

A series of (S)-(+)-camphor-based growth hormone (GH) secretagogues was synthesized to study the structure-activity relationships of the screening lead L-368,112. The stereoisomer bearing the (R)-nipecotic acid amino side-chain was considerably more active than its (S)-counterpart in the rat GH release assay. N-terminal amino acid derivatization with a (R)-(2-hydroxy)propyl substituent resulted in a secretagogue of approximate equal potency to the benzolactam L-692,429. Use of other N-terminal amino acids, especially ones that have yielded highly active secretagogues in both the benzolactam and spiropiperidine series, gave analogs of greatly diminished intrinsic activity. Replacement of the spiroindanyl piperidine of L-368,112 with an *o*-tolyl piperazine provided analogs of comparable GH releasing activity in vitro.

Acknowledgement

We would like to thank Dr. Peter Williams of Merck West Point for many helpful suggestions for the synthesis of intermediates **7** and **23**.

References

1. Bowers, C. Y.; Momany, F. A.; Reynolds, G. A.; Hong, A. *Endocrinology* **1984**, *114*, 1537.
2. (a) Smith, R. G.; Cheng, K.; Schoen, W. R.; Pong, S. S.; Hickey, H.; Jacks, T.; Butler, B.; Chan, W. -S.; Chaung, L. Y.-P.; Judith, F.; Taylor, J.; Wyvratt, M. J.; Fisher, M. H. *Science* **1993**, *260*, 1640.; (b) Schoen, W. R.; Pisano, J. M.; Wyvratt, M. J.; Fisher, M. H.; Prendergast, K.; Cheng, K.; Can, W. W.-S.; Butler, B.; Smith, R. G.; Ball, R. G. *J. Med. Chem.* **1994**, *37*, 897.
3. Patchett, A. A.; Nargund, R. P.; Tata, J. R.; Chen, M.-H.; Barakat, K.J.; Johnston, D. B. R.; Cheng, K.; Chan, W. W.-S.; Butler, B.; Hickey, G.; Jacks, T.; Schleim, K.; Pong, S.-S.; Chaung, L.-Y. P.; Chen, H. Y.; Frazier, E.; Leung, K. H.; Chiu, S. -H. L.; Smith, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, 92, 7001.
4. Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Wong, E. H. F. *J. Med. Chem.* **1992**, *35*, 2033.
5. Evans, B. E.; Lundell, G. F.; Cilbert, K. F.; Bock, M. G.; Rittle, K. E.; Carroll, L; Williams, P. D.; Pawluczyk, J. M.; Leighton, J. L.; Young, M.; Erb, J. M.; Hobbs, D. W.; Gould, N. P.; DiPardo, R. M.; Hoffman, J. B.; Perlow, D. S.; Whitter, W. L.; Veber, D. F.; Pettibone, D. J.; Clineschmidt, B. V.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem.* **1993**, *36*, 3993.
6. Hanessian, S.; Kloss, H. *Tetrahedron Lett.* **1985**, *26*, 1261.
7. (a) Schoen, W. R.; Ok, D.; DeVita, R. J.; Pisano, J. M.; Hodges, P.; Cheng, K.; Chan, W. W.-S.; Butler, B. S.; Smith, R. G.; Wyvratt, M. J.; Fisher, M. H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1117. (b) Ok, D.; Schoen, W. R.; Hodges, P.; DeVita, R. J.; Brown, J. E.; Cheng, K.; Chan, W. W.-S.; Butler, B.; Smith, R. G.; Fisher, M. H.; Wyvratt, M. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2709.
8. Williams, P. D.; Anderson, P. S.; Ball, R. G.; Bock, M. G.; Carroll, L. A.; Chiu, S. L.; Clineschmidt, B. V.; Culberson, J. C.; Erb, J. M.; Evans, B. E.; Fitzpatrick, S. L.; Freidinger, R. M.; Kaufmann, D. S.; Gundell, G. F.; Murphy, J. S.; Pawluczyk, J. M.; Perlow, D. S.; Pettibone, D. J.; Pitzenberger, S. M.; Thompson, K. L.; Veber, D. F. *J. Med. Chem.* **1994**, *37*, 565.
9. Cheng. K.; Chan, W. W.-S.; Barreto, A.; Conver, E. M.; Smith, R. G. *Endocrinology* **1989**, *124*, 2791.

(*Received in USA* 17 *April* 1996; *accepted* 9 *May* 1996)