Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 24, pp. 2877-2882, 1994
Copyright © 1994 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0960-894X/94 $7.00+0.00

0960-894X(94)00438-2

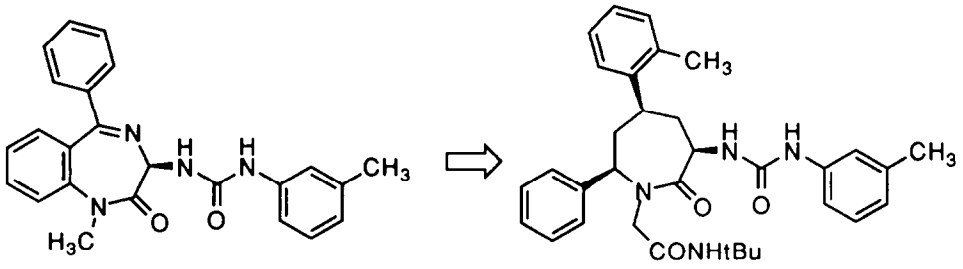
5,7-Diphenyl-3-ureidohexahydroazepin-2-ones as Cholecystokinin-B Receptor Ligands

John A. Lowe, III*, Weimin Qian, Pamela J Scott, Stafford McLean, Dianne K. Bryce, Rosemary T. Crawford, Jon Bordner

Central Research Division, Pfizer Inc
Eastern Point Road, Groton, CT 06340

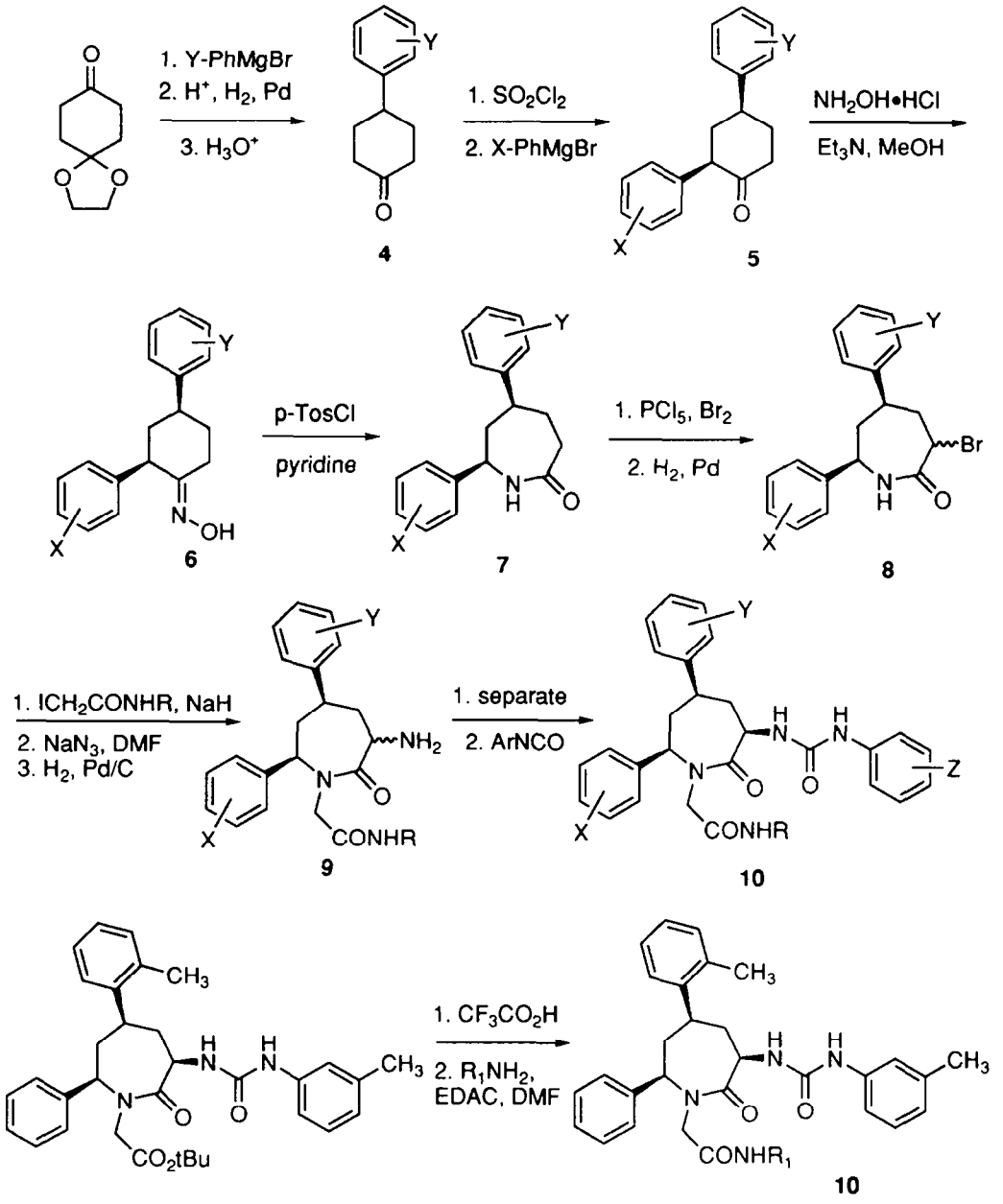
Abstract: A series of 5,7-diphenyl-3-ureidohexahydroazepin-2-one cholecystokinin-B (CCK-B) receptor antagonists was synthesized using Beckmann ring expansion of a suitable 2,4-diphenylcyclohexanone as a key step. SAR studies revealed the importance of the 5-aryl group for high and selective CCK-B receptor affinity, as illustrated in compound (-)-**10i** (CCK-B IC_{50} = 6.8 nM).

The discovery that CCK-4, a selective ligand for the cholecystokinin-B (CCK-B) receptor, causes panic behavior in humans set the stage for the development of CCK-B antagonists as novel therapeutants for panic disorder and anxiety.[1] Subsequent studies have suggested CCK-B receptors may be involved in pain[2] and control of central dopaminergic function.[3] While CCK-B antagonists have been developed from numerous structural classes,[4] one of the most versatile is the benzodiazepine family, represented by the potent and selective CCK-B antagonist L-365,260, **1**, below.[5] In a search for alternatives to the benzodiazepine nucleus, we chose the 5,7-diphenylhexahydroazepin-2-one structure for investigation, and report our SAR studies leading to the high affinity CCK-B receptor ligand **10i** herein.



L 365,260, **1** **10i**

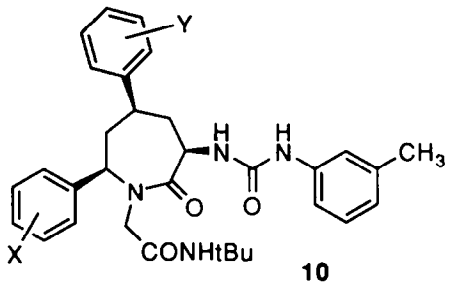
The preparation of the 3-ureido-5,7-diphenylhexahydroazepin-2-one system is outlined in Scheme 1. The key step for construction of the azepin-2-one nucleus is the Beckmann ring expansion reaction of oxime **6**. Its precursor, ketone **5**, was prepared by addition of an aryl Grignard reagent to the 2-chloro derivative of ketone **4**, derived from the monoethylene ketal of cyclohexane-1,4-dione by addition of an aryl Grignard reagent followed by hydrogenolysis and hydrolysis. To introduce the ureido and amide side chains, dibromination at the 3-position was followed by treatment with palladium-on-carbon in the presence of quinoline and hydrogen to selectively remove one bromine. Addition of the acetamido side chain by N-1 alkylation, followed by



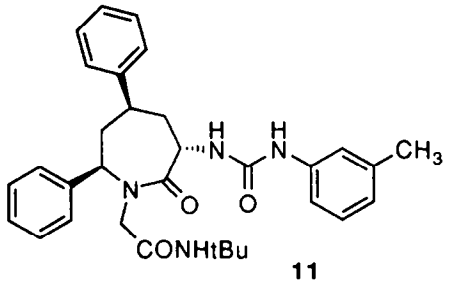
Scheme 1. Preparation of 5,7-diarylhexahydroazepin-2-ones **10**.

displacement of the C-3 bromide with azide, and reduction to the corresponding amine then produced a separable mixture of diastereomers; acylation afforded the final products **10**.[6] Determination of the stereochemistry was carried out by X-ray analysis of single crystals of compound **10m** [7] Correlation of the stereochemistry with the other compounds **10** was facilitated by the characteristic ^{1}H-NMR AB quartet signal for the methylene group between N-1 and the amide group for each diastereomer.[6] Resolution was carried out by forming the t-BOC-L-phenylalanine derivative of **9i**, followed by removal of the t-BOC group and separation of diastereomers by column chromatography Edman degradation to remove the L-phenylalanine group provided the separate enantiomers of **9i**, and acylation then provided the enantiomers (+)- and (-)-**10i**.[8]

Table 1 CCK SAR at the 5- and 7-positions in 5,7-diphenyl-3-ureidohexahydroazepin-2-ones.



10



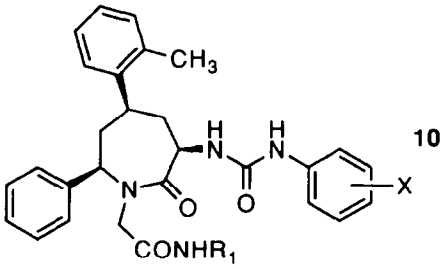
11

CPD.	X	Y	CCK-B, IC_{50}[9]	CCK-A, IC_{50}[9]
10a	H	H	16 ± 4.4	823 ± 206
10b	4-F	H	203 ± 33	2,800 ± 1,200
10c	3-F	H	31 ± 0 67	1,000 ± 290
10d	4-CH_3	H	560 ± 57	970 ± 250
10e	3-CH_3	H	141 ± 49	1,600 ± 500
10f	H	4-F	65 ± 0.33	700 ± 120
10g	H	4-CH_3	190 ± 40	1,100 ± 320
10h	H	3-CH_3	66 ± 2.2	1,300 ± 383
10i	H	2-CH_3	7.8 ± 2.7	580 ± 77
10j	H	2-CH_2CH_2	25 ± 3.8	810 ± 130
10k	H	2-OCH_3	28 ± 6.9	750 ± 40
11	H	H	450 ± 160	>10,000
(+)-**10i**	H	2-CH_3	527 ± 210	610 ± 95
(-)-**10i**	H	2-CH_3	6.8 ± 1.9	930 ± 290
L-365,260			8.1 ± 1 5	86 ± 27

SAR around the 5- and 7-phenyl rings (above) shows little room for variation on either ring, with the exception of the 2-tolyl ring at the 5-position, compound **10i** The improved CCK-B receptor affinity of **10i** would seem to result from a conformational effect on the hexahydroazepin-2-one nucleus rather than a

stereoelectronic or lipophilicity effect, since the 3- and 4-methyl substituents in **10g** and **10h** decrease CCK-B receptor affinity relative to **10a**. Other 2-substituted 5-phenyl groups, as in **10j** and **10k**, showed decreased CCK-B receptor affinity relative to **10i**, confirming the tight SAR in this region, and suggesting that this proposed conformational effect is not increased by a larger 2-substituent The importance of the spatial relationship between the *cis* 5,7-diphenyl template and the 3-ureido side chain for CCK-B receptor affinity is illustrated by lack of CCK-B affinity of diastereomer **11**, alternative diastereomers with *trans*-oriented 5,7-diphenyl groups were not examined Resolution of **10i** demonstrates that the (-) isomer possesses the higher CCK-B receptor affinity, again demonstrating the specificity of the interaction between the 5,7-diphenylhexahydroazepin-2-one template and the CCK-B receptor. The flexibility of the SAR of the amide and ureido groups is indicated below, the N-(1-methyl)cyclohexyl and N-2-chlorophenyl amide, prepared as indicated at the bottom of Scheme 1, and the 3-trifluoromethyl and 3-nitrophenylureido side chains provide compounds with high and selective CCK-B receptor affinity

Table 2. CCK SAR at the N-1 and C-3 ureido positions in 5,7-diphenylhexahydroazepin-2-ones



CPD	R_1	X	CCK-B, IC_{50}[9]	CCK-A, IC_{50}[9]
10i	tBu	3-CH_3	7 8 ± 2 7	583 ± 77
10l	(1-CH_3)c-hexyl	3-CH_3	13 4 ± 4.4	1,300 ± 230
10m	(1-CH_3)c-hexyl	3-CH_2CH_3	38 ± 7.8	>10,000
10n	$CH(tBu)_2$	3-CH_3	453 ± 62	>10,000
10t	2-propyl	3-CH_3	80 ± 19	560 ± 110
10u	(2-Cl)Ph	3-CH_3	28 ± 6.6	1,100 ± 290
10v	(3-Cl)Ph	3-CH_3	79 ± 38	>10,000
10w	(4-Cl)Ph	3-CH_3	278 ± 131	>10,000
10x	(2-CH_3)Ph	3-CH_3	71 ± 8 4	1,100 ± 230
10y	(4-CH_3)Ph	3-CH_3	40 ± 1.2	>10,000
10o	tBu	3-CF_3	28 ± 5 8	2500 ± 740
10p	tBu	4-Cl	117 ± 12	>10,000
10q	tBu	3-F	36 ± 5.1	1,800 ± 380
10r	tBu	4-OCH_3	87 ± 12	2,200 ± 360
10s	tBu	3-NO_2	10 ± 1 2	>10,000
L-365,260			8.1 ± 1 5	86 ± 27

The strategy of altering the benzodiazepine template of **1** to a 5,7-diphenylhexahydroazepin-2-one affords compounds with comparably high and selective affinity for the CCK-B receptor. This 5,7-diphenylhexahydroazepin-2-one structure thus provides a new "template" for CCK-B receptor ligands, joining the collection of "privileged structures" previously described in this area.[10] By expanding the library of "privileged structures" and their SAR, chemists may provide tools for understanding the mechanism of receptor antagonism while at the same time enabling more efficient discovery of antagonists at new receptors.

Acknowledgment

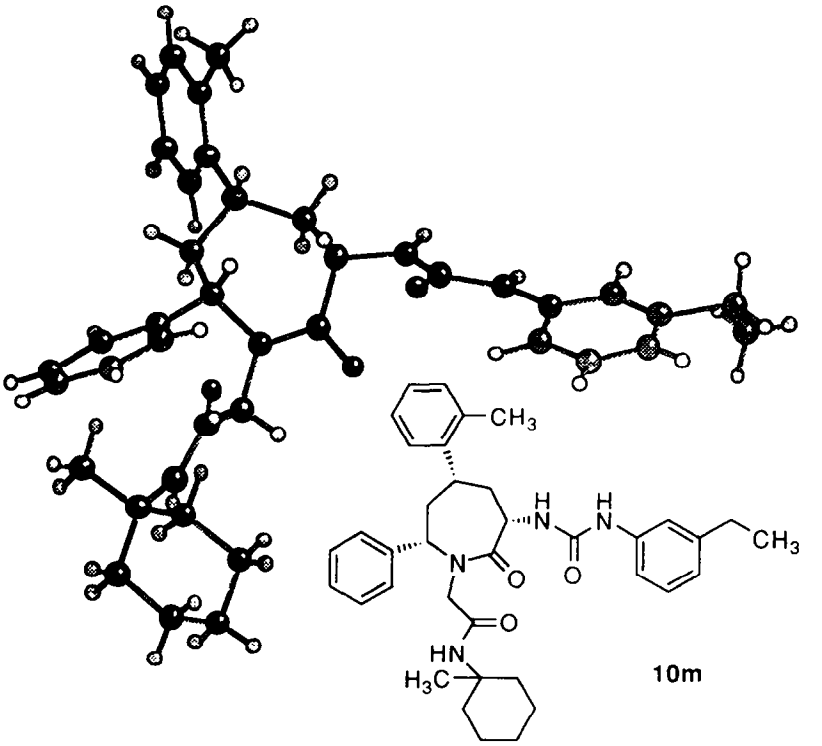
The authors wish to thank Dr. Jim Heym and Dr. Jeff Ives for their support and encouragement.

References and Notes

1. Dooley, D.J ; Klamt, I. *Psychopharmacol.* **1993**, *112*, 452-454.
2. Noble, F., Derrien, M.; Roques, B.P *Br. J. Pharmacol.* **1993**, *109*, 1064-1070
3. Rasmussen,K., Czachura, J.F., Stockton, M.E , Howbert, J J *J. Pharmacol. Exp. Ther.*, **1993**, *264*, 480-488.
4. Makovec, F. *Drugs Future*, **1993**, *18*, 919-931.
5 Bock, M, DiPardo, R.M ; Evans, B.E.; Rittle, K.E.; Whitter, W.L., Garsky, V M ; Gilbert, K.F., Leighton, J.L , Carson, K.L.; Mellin, E.C., Veber, D.F.; Chang, R.S.L.; Lotti, V.J , Freedman, S.B.; Smith, A.J.; Patel, S., Anderson, P S.; Freidinger, R.M. *J. Med. Chem.* **1993**, *36*, 4276-4292.
6 Analytical data for **10i**: mp 253-253.5°C. ^{1}H-NMR (δ, $CDCl_3$) 1.26 (singlet, 9H), 1 7-2.6 (multiplets, 5H), 2.23 (s, 3H), 3.64 (m, 1H), 3.80 (AB_q, J_{AB} = 16, Δν=399, 2H, this is the signal which is diagnostic for the *cis* diastereomer, as confirmed by the X-ray structure of compound **10m** below), 4.14 and 4.6-4.8 (multiplets, 2H), 6.57 (d, J=9, 1H), 6.70 (d, J=7, 1H), 7.0-7 6 (m, 10H), 8.33 (broad singlet, 1H). IR (cm.$^{-1}$, KBr): 1673 and 1640 (C=O). MS (%): 526 (parent, <1), 235 (73), 234 (82), 193 (36), 132 (100), 57 (32), 43 (46), 41 (32). Anal Calc'd. for $C_{32}H_{38}N_4O_3$: C 72 98, H 7.27, N 10 64. Found. C 72.94, H 7.31, N 10.45.
7 A representative crystal was surveyed and a 1 Å data set (maximum sin Θ/λ = 0.5) was collected on a Nicolet R3m/μ diffractometer. Atomic scattering factors were taken from the International Tables for X-ray Crystallography (International Tables for X-ray Crystallography, Vol IV, pp. 55, 99, 149, Birmingham: Kynoch Press, 1974). All crystallographic calculations were facilitated by the SHELXTL (G.M. Sheldrick; SHELXTL. User Manual, Nicolet Instrument Co., 1981.) system All diffractometer data were collected at room temperature. A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and the hydrogen on nitrogen were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0 1 of their corresponding standard deviations. The final R-index was 7 55% A final difference Fourier revealed no missing or misplaced electron density. The refined structure, plotted using the Nemesis program © Oxford Molecular, Ltd., is shown below, compound **10m**
8. Rittle, K.E.; Evans, B.E.; Bock, M.G.; DiPardo, R M ; Whitter, W.L., Hommick, C F , Veber, D.F.; Freidinger, R M. *Tet. Let.* **1987**, *28*, 521-522.
9 **CCK-B Binding Assay**· The tissue for the assay was prepared by dissecting the cortex from a male Hartley guinea pig and homogenizing 15 strokes with a Teflon homogenizer in 20 vols 50 mM Tris HCl pH 7.4 with 5 mM MnCl2 at 4°C The homogenate was centrifuged at 4°C for 30 min at 100,000g The pellet was resuspended in the same buffer and centrifuged as before. The final pellet was diluted to a concentration of 10 mg/mL with assay buffer and kept refrigerated
The buffer for the assay consisted of 10 mM HEPES, 5 mM MgCl2, 1 mM EGTA, 130 mM NaCl, 0 2 mg/mL bacitracin, at pH 6 5 and room temperature, with 0 5 mg/mL bovine serum albumin added before incubation was begun. The test drugs were made up at 1 mM in 100% dimethylsulfoxide (DMSO) and diluted

to test concentration using 4% DMSO so as to give a concentration of 1% DMSO in the final assay mixture. The incubation mixture consisted of 50 uL tissue preparation, 100 uL of a solution of 125-I-BH-CCK-8 (NEX 203, 2200 Ci/mmol) at 50 pM, 20 uL of the test drug solution (or a 1 uM solution of CI-988, the standard CCK-B antagonist L-365,260 [Showell, G A , Bourrain, S.; Neduvelil, J G , Fletcher, S R , Baker, R ; Watt, A P., Fletcher, A E.; Freedman, S.B.; Kemp, J A ; Marshall, G.R ; Patel, S., Smith, A.J., Matassa, V.G. *J. Med. Chem.*, **1994**, *37*, 719-721] as a blank, or vehicle as a control), and 30 uL of the assay buffer with 4% DMSO. The incubation was initiated by adding tissue preparation and continued at room temperature for 2 hr. It was then terminated by spinning the plate containing the incubation in a H1000B rotor fitted on a Sorvall RT6000 refrigerated centrifuge at 4°C for 5 min at 3000 rpm. The supernatant was discarded and the pellet washed with 200 uL of wash buffer, then recentrifuged The supernatant was again decanted, and the pellet harvested onto Betaplate filters which had been soaked in 0.2% polyethyleneimine for a minimum of 2 hr, using a Skatron cell harvester at setting 222 using 50 mM Tris HCl pH 7 4 as the wash buffer. The filtermats were counted on a Betaplate counter for 45 sec per sample. Data were analyzed and results are reported as IC50 values based on six concentrations done in at least three separate experiments CCK-A binding was carried out in a similar fashion using guinea pig pancreas as the tissue source of the receptor.

10 Evans, B.E ; Rittle, K.E., Bock, M G., DiPardo, R.M.; Freidinger, R M , Whitter, W.L , Lundell, G.F.; Veber, D.F , Anderson, P S ; Chang, R S.L , Lotti, V.J , Cerino, D J , Chen, T B ; Kling. P J , Kunkel, K A., Springer, J P ; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235-2246



10m

(*Received in USA* 10 *October* 1994; *accepted* 9 *November* 1994)