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A Water Soluble Benzazepine Cholecystokinin-B Receptor Antagonist

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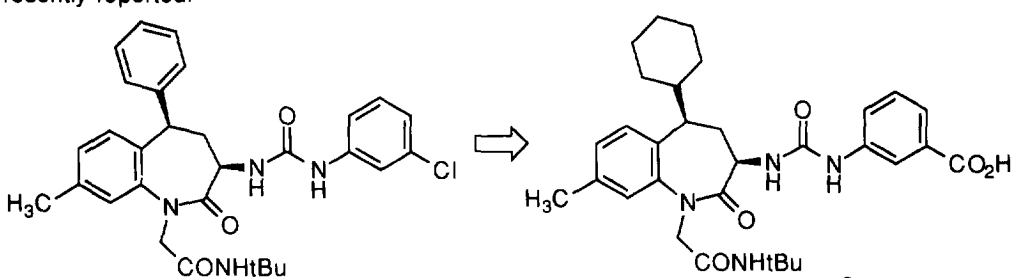
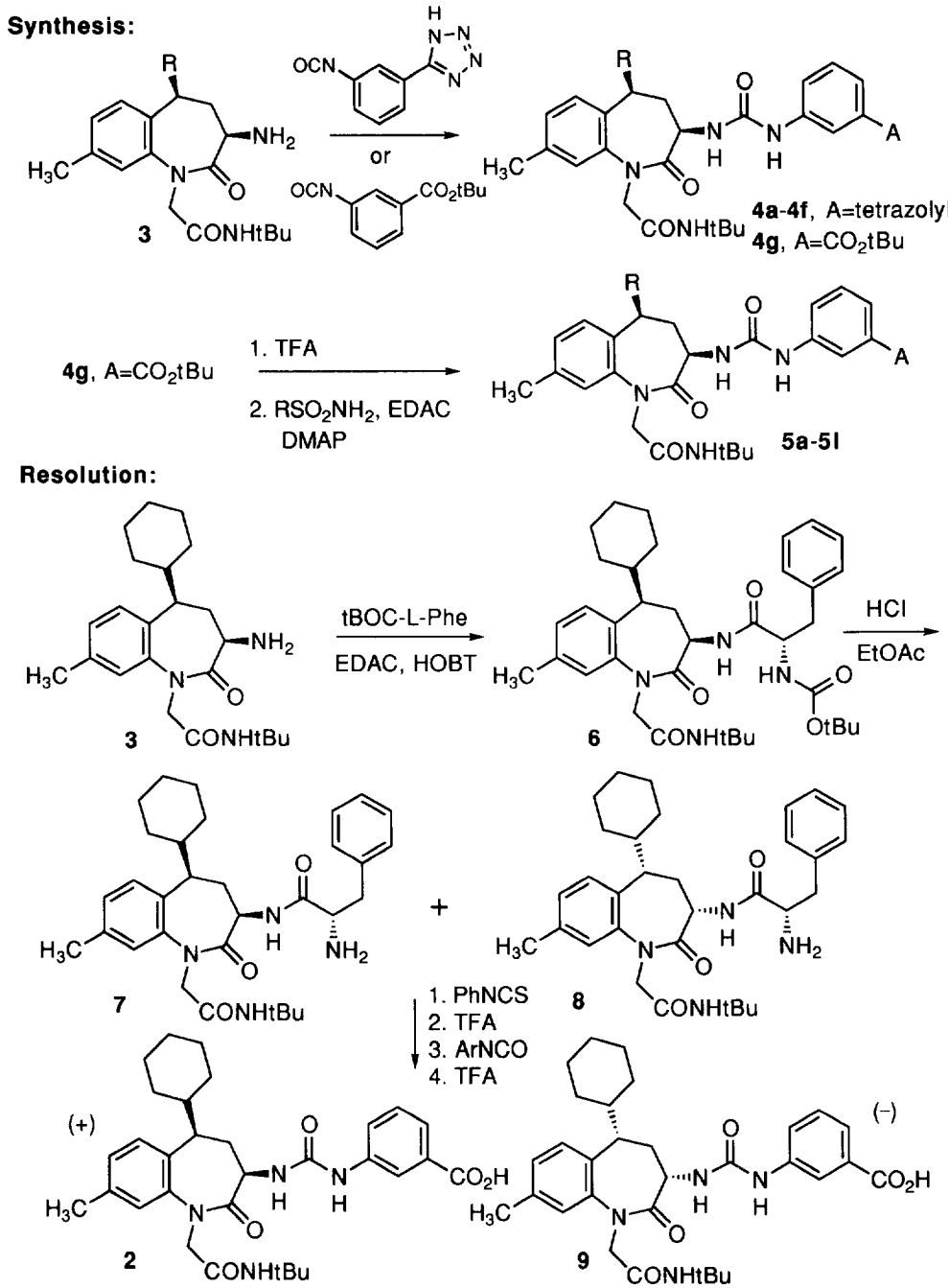
Abstract: A series of 5-substituted-3-ureidobenzazepin-2-ones bearing ionizable functionality was synthesized as potential cholecystokinin-B (CCK-B) receptor antagonists. SAR of this series of compounds demonstrated the optimal combination of a carboxylic acid and 5-cyclohexyl group, providing the high affinity (CCK-B IC_{50} = 0.10 nM), water soluble CCK-B antagonist **2**.

Antagonists at the cholecystokinin-B (CCK-B) receptor have potential as therapeutic agents for panic disorder and anxiety,[1] pain,[2] and control of central dopaminergic function.[3] We recently described the synthesis and SAR of a series of potent and selective CCK-B receptor antagonists exemplified by **1** below.[4] Despite its potent and selective CCK-B receptor affinity, the low water solubility of **1** is a drawback to its potential application to the study of CCK pharmacology. Modification of **1** with ionizable groups was thus initiated with both carboxylic acids and "acid surrogates" such as acyl sulfonamides and tetrazoles. Optimizing the combination of these ionizable groups with the substituent at the 5-position of the benzazepin-2-one ring led to the potent, selective, and water soluble CCK-B antagonist **2**. A similar use of ionizable groups to improve the water solubility of a series of benzodiazepinone CCK-B receptor antagonists was recently reported.[5]



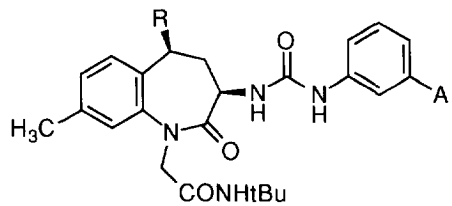
The SAR leading to **2** was developed by synthesis of ionizable compounds **4a-4f** and **5** from the 3-aminobenzazepin-2-one precursor **3** described in our previous work (Scheme 1).[4] A new reagent, 3-(5-tetrazolyl)phenyl isocyanate, prepared from the corresponding benzoic acid with diphenyl phosphoryl azide, was employed to install the 3-(5-tetrazolyl)phenylureido side chain in compounds **4a-4f**.[6] The inertness of the tetrazolyl group during these operations obviated the need for a protecting group. The potential for epimerization at the C-3 (ureido) position during the



Scheme 1. Synthesis and resolution of ionizable benzazepin-2-one CCK-B antagonists. Absolute stereochemistry is arbitrarily depicted.

conversion of **4g** to **5** was avoided by using the readily removed t-butyl ester protecting group and mild, water-soluble carbodiimide, coupling conditions.

Table 1. SAR of Ionizable 5-Substituted -3-ureidobenzazepin-2-ones.



CPD.	A	R	CCK-B, IC_{50}[4]	CCK-A, IC_{50}[4]
4a	5-Tetrazolyl	Ph	0.81 ± 0.22	620 ± 120
4b	5-Tetrazolyl	2-propyl	0.98 ± 0.12	250 ± 30
4c	5-Tetrazolyl	CH_2Ph	1.7 ± 0.31	34 ± 12
4d	5-Tetrazolyl	CH_2(c-hexyl)	0.88 ± 0.06	220 ± 29
4e	5-Tetrazolyl	(4-CH_3)Ph	9.0 ± 0.70	600 ± 70
4f	5-Tetrazolyl	c-hexyl	0.22 ± 0.04	490 ± 130
5a	CO_2CH_3	Ph	1.4 ± 0.39	310 ± 55
5b	CO_2H	Ph	2.7 ± 0.73	4,200 ± 290
5c	$CONHSO_2Ph$	Ph	4.8 ± 1.8	1,300 ± 380
5d	$CONHSO_2CH_3$	Ph	0.88 ± 0.23	970 ± 230
5e	$CONHSO_2CH_2Ph$	Ph	4.2 ± 1.1	730 ± 140
5f	$CONHSO_2CH_2CH_3$	Ph	1.0 ± 0.06	1,100 ± 250
5g	$CONHSO_2$(2-CH_3)Ph	Ph	7.9 ± 3.1	1,300 ± 200
5h	$CONHSO_2CF_3$	Ph	5.1 ± 1.7	320 ± 72
5i	CONH(5-Tetrazolyl)	Ph	0.7 ± 0.15	1,000 ± 220
5j	CO_2CH_3	c-hexyl	0.60 ± 0.15	370 ± 75
5k	CO_2H	c-hexyl	0.20 ± 0.013	2,300 ± 220
5l	$CONHSO_2CH_3$	c-hexyl	0.26 ± 0.075	520 ± 34
1	Cl	Ph	0.48 ± 0.079	180 ± 50
2	CO_2H (+)	c-hexyl	0.10 ± 0.015	1400 ± 240
L-365,260			8.1 ± 1.5	86 ± 27

Compared to compound **1**, the carboxylate analog **5b** shows only slightly reduced affinity for the CCK-B receptor in guinea pig cortex and moderate selectivity over the CCK-A receptor in guinea pig pancreas. The increased CCK-B receptor affinity of the methyl ester precursor **5a** indicates that ionizability *per se* is permitted but is not as important as electron-withdrawing ability for receptor affinity. Examination of "acid surrogates" to probe the effect of increasing size of the ionizable function on CCK-B receptor affinity showed that the methyl and ethyl sulfonamides **5d** and **5f**, and the tetrazole **4a**, afford similar or improved affinity relative to **5b**, whereas larger groups found in **5c**, **5e**, and **5g** decrease CCK-B receptor affinity. Using the 5-tetrazolyl group on the ureido side chain,

SAR at the 5-position of the benzazepin-2-one was next investigated, resulting in selection of the 5-cyclohexyl group in compound **4f** as optimal. Based on its improved selectivity relative to **4f**, the 5-cyclohexyl carboxylate analog **5k** was selected for resolution, affording **2** (Scheme 1). Compared with **1**, compound **2** shows both increased solubility (3 mg/mL for **2** (as the potassium salt)*vs.* 0.0002 mg/mL for **1**) and *in vivo* efficacy (pentagastrin-induced acid secretion model,[4] ED_{50} = 0.03 mg/kg s.c. for **2** *vs.* 0.8 mg/kg s.c. for **1**). Thus, incorporation of a carboxylic acid, as well as other ionizable groups, into the 5-substituted 3-ureido benzazepin-2-one compounds provides potent, selective, and water soluble CCK-B receptor antagonists.

Acknowledgment

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6. 3-Tetrazolylbenzoic acid: 3-Cyano benzoic acid was converted to the corresponding methyl ester using acetyl chloride in methanol at 55 °C for 12 hr in 76% yield. ^{1}H-NMR (δ, $CDCl_3$): 3.93 (s, 3H), 7.56 (t, J=7, 1H), 7.82 (m, 1H), 8.23 (m, 1H), 8.30 (m, 1H). IR (neat): 2228 (CN) cm^{-1}. The nitrile was then converted to the corresponding tetrazole using 2.5 equiv of trimethylstannyl azide in refluxing xylene for 3 h. The crude residue (particle beam MS showed P=205 for parent+1 peak, IR showed no peak at 2228 cm^{-1}) was converted to the corresponding carboxylic acid using lithium hydroxide in water /methanol/tetrahydrofuran at rt in 91% yield. ^{1}H-NMR (δ, $CDCl_3$): 7.70 (t, J=8, 1H), 8.22 (m, 2H), 8.69 (bs, 1H). IR (neat): 1671 (C=O) $cm.^{-1}$. MS (particle beam, %): 208 (parent+$NH4^+$, 100), 191 (parent+1, 20).

Conversion to the isocyanate was accomplished using 1 equivalent of diphenyl phosphoryl azide and 2 equivalents of triethylamine in refluxing benzene for 1 h; this was followed by addition of **3** and continued refluxing for 12 hr to furnish compounds **4a** to **4f** in yields of 48 to 78%.

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