Articles

Methods for Drug Discovery: Development of Potent, Selective, Orally Effective Cholecystokinin Antagonists†

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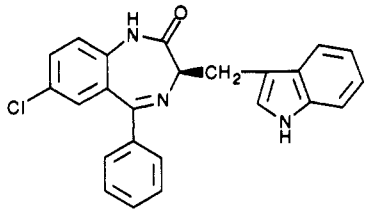
3-(Acylamino)-5-phenyl-2*H*-1,4-benzodiazepines, antagonists of the peptide hormone cholecystokinin (CCK), are described. Developed by reasoned modification of the known anxiolytic benzodiazepines, these compounds provide highly potent, orally effective ligands selective for peripheral (CCK-A) receptors, with binding affinities approaching or equaling that of the natural ligand CCK-8. The distinction between CCK-A receptors on the one hand and CNS (CCK-B), gastrin, and central benzodiazepine receptors on the other is demonstrated by using the structure–activity profiles of the new compounds. Details of the binding of these agents to CCK-A receptors are examined, and the method of development of these compounds is discussed in terms of its relevance to the general problem of drug discovery.

In an earlier paper,[1] we summarized a program of design and synthesis of new, highly potent, orally effective, nonpeptidal antagonists of the peptide hormone cholecystokinin (CCK). These compounds, 3-substituted 1,4-benzodiazepines (e.g., 1 and 2), were obtained by reasoned modification of the known anxiolytic benzodiazepines. They provide novel examples of effective, nonpeptidal ligands for a peptide receptor which have been generated by a program of deliberate design. They include 3-alkyl compounds, such as the prototype 1, and 3-amido compounds such as L-364,718, 2. The latter compound is a selective, orally effective antagonist for peripheral (CCK-A[2]) receptors[3] currently under investigation as a potential therapeutic agent.



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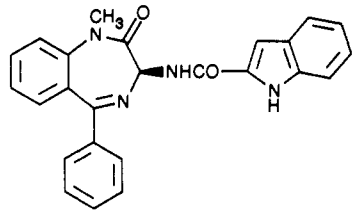

2

The importance of CCK, the shortage of suitable antagonists for its study, and our efforts to develop new agents to remedy this shortage were described in detail in an earlier publication.[4] That publication elaborated the design, synthesis, and structure/activity profile of the 3-alkylbenzodiazepine class of CCK antagonists represented by the prototype 1. Continuing investigation of that lead structure provided the considerably more potent 3-amidobenzodiazepine CCK antagonists which include L-364,718 (2). The purposes of this report are to present the synthesis and structure/activity profile of the 3-amidobenzodiazepine class of CCK antagonists, and to consider what insights the development pathway to these compounds offers for the general problem of drug discovery.

Chemistry

The structures and in vitro activities of 3-amidobenzodiazepine CCK antagonists are presented in Tables I–III. Key intermediates in the synthesis of these agents were the 3-amino compounds, examples of which are included in Table IV. The original approach used to obtain these amines was the multistep sequence shown in Scheme I, an amalgamation of published steps, several of which provide mediocre product yields. This overall synthetic sequence was adequate for the initial small-scale investigation of the 3-amido lead series (e.g., II, III) which gave rise to 2, but proved wholly inadequate for the larger scale effort which followed the discovery of this agent and which produced the bulk of the compounds shown in Tables I–III.

For these more extensive studies, shorter, more efficient syntheses of the requisite 3-aminobenzodiazepines were developed. These have been described in detail in recent publications.[9,10] Resolution of these amines into the

† Dedicated to Prof. Edward C. Taylor on the occasion of his 65th birthday.

‡ Rahway, NJ.

(1) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4918.
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(3) Chang, R. S. L.; Lotti, V. J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4924.
(4) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Gould, N. P.; Lundell, G. F.; Homnick, C. 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.* **1987**, *30*, 1229.
(5) Sternbach, L. H.; Fryer, R. I.; Metlesics, W.; Reeder, E.; Sach, G.; Saucy, G.; Stempel, A. *J. Org. Chem.* **1962**, *27*, 3788.
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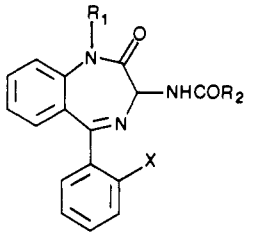
Table I. Receptor Binding Affinities for 3-(Acylamino)benzodiazepines[a]



compd	X	R_1	R_2	stereo.	IC_{50}, μM: CCK pancreas	CCK brain	gastrin
3	H	H	Boc-L-Trp	*RS*	6	20	>100
4	H	H	Boc-D-Trp	*RS*	17	>100	>100
5	H	H	3-indolyl	*RS*	1.1	8.4	18
6	H	H	CH_2-3-indolyl	*RS*	1.0	11	32
7	H	H	$(CH_2)_2$-3-indolyl	*RS*	4.8	100	17
8	H	H	$(CH_2)_3$-3-indolyl	*RS*	20	>100	
9	H	H	2-indolyl	*RS*	0.0047	8	4
10	F	H	CH_2-4-benzo[*b*]thiopheneyl	*RS*	1	3.3	3.9
11	F	H	2-(1-CH_3)-1-indenyl	*RS*	0.022	35	>10
12	F	H	*p*-Cl-phenyl	*RS*	0.006	40	14
13	F	H	2-quinazolinyl	*RS*	0.3	80	>10
14	F	H	1-OH-1-phenylmethyl	*RS*	100	80	>10
15	F	H	(*E*)-2-phenylethenyl	*RS*	0.011	5.5	3.8
16	F	H	phenylaminomethyl	*RS*	0.9	100	>10
17	F	H	2-benzofuranyl	*RS*	0.009	32	11
18	F	H	CH_3	*RS*	40	>40	>40
19	H	H	2-indolinyl		0.9	>40	110
20	H	CH_3	Boc-L-Phe	*RS*	0.7	13	26
21	H	CH_3	L-Phe	*S*	1.9	>40	>40
22	H	CH_3	L-Phe	*R*	100	>100	55
23	F	H	2-pyrrolyl	*RS*	0.11	100	25
24	H	H	2-naphthyl	*RS*	0.02	12	14
25	H	H	pyrazinyl	*RS*	>10	>100	>100
26	H	H	1-naphthyl	*RS*	1.6	12	29
27	F	CH_3	3-thienyl	*RS*	0.028[+]	26	11
28	F	H	3-thienyl	*RS*	0.15	>50	>10
29	H	H	Boc-L-Phe	*RS*	2.7	12	>100
30	H	H	L-Phe	*S*	3.1	>100	>100
31	H	CH_3	isopropyl	*S*	1.1[+]	>100	73
32	H	CH_3	3-methyl-1-butyl	*S*	0.78[+]	>100	130
33	H	CH_3	cyclohexyl	*S*	0.8[+]	>100	>100
34	H	CH_3	(*E*)-2-phenylethenyl	*S*	0.0003[+]	0.64	0.18
35	H	CH_3	*tert*-butyl	*S*	1.6	>100	13
36	H	CH_3	cyclohexyl	*R*	>10[+]	18	1.5
37	H	CH_2COOEt	H	*RS*	>100[+]	48	25
38	F	CH_3	Boc-D-Phe	*RS*	0.58[+]	2.7	2.9
39	F	CH_3	Boc-D-Phe	*S*	0.34[+]	1.0	1.2
40	H	H	*p*-Cl-phenyl-CH_2	*RS*	1.3[+]	2.9	7
41	H	CH_3	*m*-CH_3O-phenyl-CH_2	*S*	0.33[+]	2.1	0.42
42	H	CH_3	*m*-CH_3O-phenyl-CH_2	*R*	45[+]	1.5	0.45

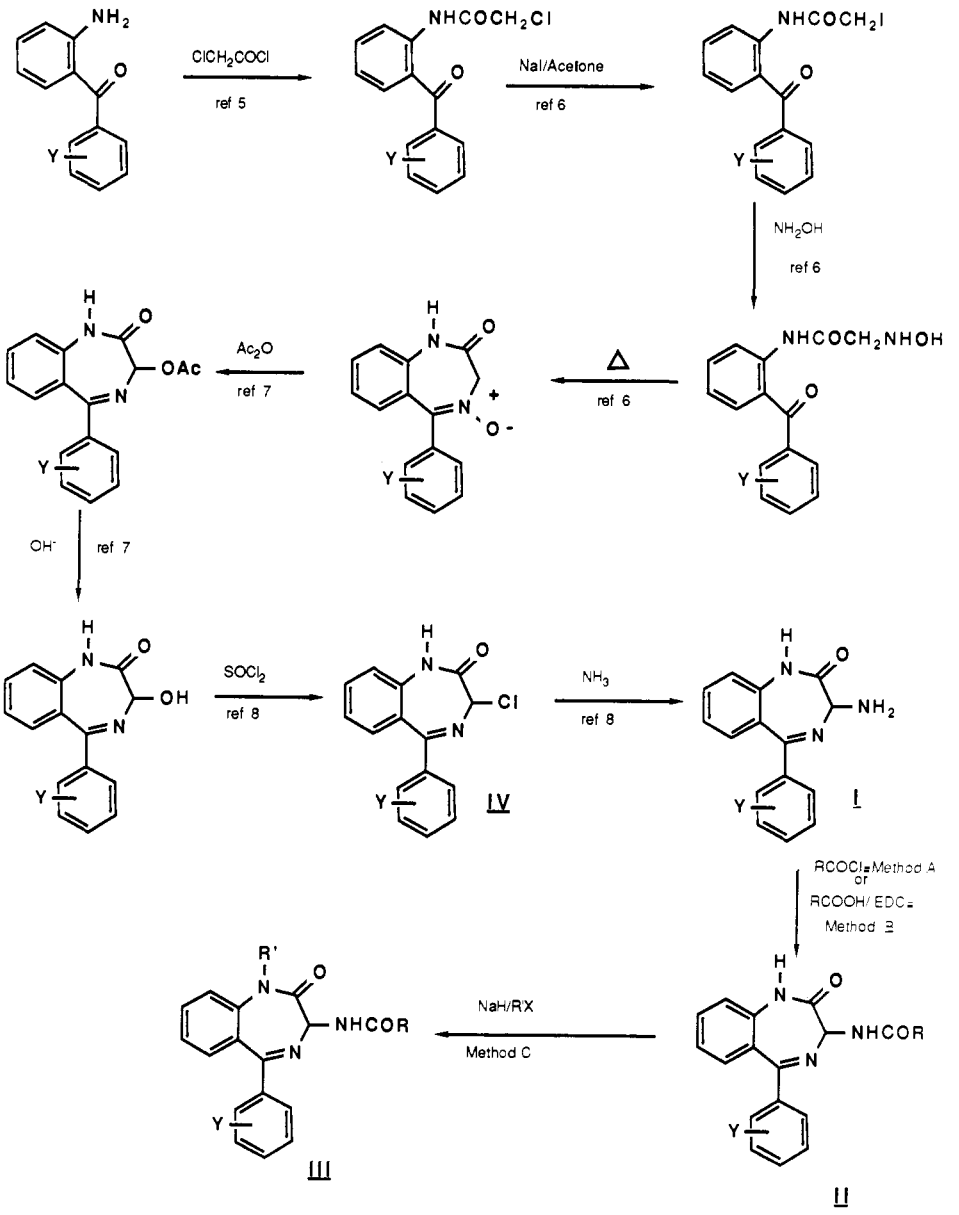
[a] Receptor binding is expressed as IC_{50}, the concentration (μM) of compound required for half-maximal inhibition of binding of [^{125}I]C-CK-33 or [^{125}I]CCK-8 (+) to CCK receptors in rat pancreatic or guinea pig brain tissues, or for half-maximal inhibition of binding of [^{125}I]gastrin to guinea pig gastric glands.[3,15]

constituent enantiomers by conventional diastereomeric salt crystallization was not readily accomplished: without seeds, the crystallization process was consistently thwarted by steady decomposition of the modestly acid-labile amine over extended times. An alternate approach involving covalent attachment of the resolving acid was therefore developed. This method, described in an earlier communication,[11] involved coupling of the target amine to a chiral α-amino acid (in this case, D- or L-Phe) to provide the diastereomeric amides. These were separated either by chromatography or by crystallization and then cleaved to provide the individual amine enantiomers by Edman degradation.[12]

The amides shown in Tables I–III were all prepared by acylation of these 3-aminobenzodiazepines either with known acid chlorides (method A) or with the free acids in the presence of a suitable coupling agent such as 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC;

(7) Bell, S. C.; Childress, S. J. *J. Org. Chem.* **1962**, *27*, 1691.
(8) Bell, S. C.; U.S. Patent 3,198,789; *Chem. Abstr.* **1965**, *63*, 18129f.
(9) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M. *Tetrahedron Lett.* **1987**, *28*, 939.
(10) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M.; Hirshfield, J.; Springer, J. *J. Org. Chem.* **1987**, *52*, 3232.
(11) Rittle, K. E.; Evans, B. E.; Bock, M. G.; DiPardo, R. M.; Whitter, W. L.; Homnick, C. F.; Veber, D. F.; Freidinger, R. M. *Tetrahedron Lett.* **1987**, *28*, 521.
(12) (a) Edman, P. *Acta Chem. Scand.* **1950**, *4*, 283. (b) Laursen, R. A.; Machleidt, W. In *Methods of Biochemical Analysis*; Glick, D., Ed.; Wiley: New York, 1980; Vol. 26, p 201.

Scheme I



method B). N^1-Substituents were added by sodium hydride/alkyl halide alkylation of a precursor II, either an amide (method C) or a benzylcarbamate (method D). N^1-Methyl compound **2** was also prepared via a two-step amine synthesis involving nitrosation/reduction of a readily available benzodiazepine.[13] Combined with a crystallization-induced asymmetric transformation which converts the racemic aminobenzodiazepine entirely to the desired *S*-isomer **128**, this method has been developed into a highly efficient route to **2** operable on a kilogram scale. Details have been presented in a recent publication.[14]

The alkylamines of Table IV were prepared by displacement of chloride from an intermediate such as IV prepared as in Scheme I. The indole *N*-methyl (**45**, **51**, **56**) was added by a repeat application of the alkylation methods C/D to the precursor amides (**44**, **50**, **43**, respectively). Physical data for the compounds of Tables I–IV are presented in Table V.

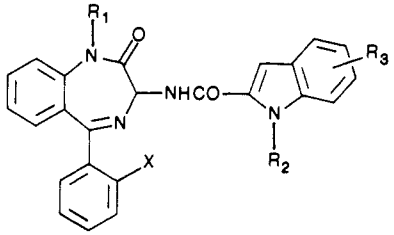
Biology

The methods employed for determination of [^{125}I]CCK-33 or [^{125}I]CCK-8 binding to rat pancreas and guinea pig cortex, [^{125}I]gastrin (human gastrin 1–17) binding to guinea pig gastric glands, and [^{3}H]diazepam or [^{3}H]flunitrazepam binding in rat and guinea pig brain, respectively, were as described previously.[3,15] Values shown are the means of triplicate determinations. The [^{125}I]CCK-33 and [^{125}I]CCK-8 assays give indistinguishable results for compounds with IC_{50} greater than ca. 1 nM. For compounds with higher affinities, the [^{125}I]CCK-33 assay tends to underestimate affinity due to the use of higher receptor concentrations in this procedure.

The in vivo activities of the compounds were determined on the basis of their abilities to antagonize CCK-8 inhibition of charcoal meal gastric emptying in mice as described previously.[16] The mice were administered the test com-

(13) (a) Sternbach, L. H.; Fryer, R. I.; Metlesics, W.; Reeder, E.; Sach, G.; Saucy, G.; Stempel, A. *J. Org. Chem.* **1962**, *27*, 3788. (b) Reference 14, footnote 6a.
(14) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 957.
(15) Chang, R. S. L.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schonberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science (Washington, D.C.)* **1985**, *230*, 177.
(16) Lotti, V. J.; Cerino, D. J.; Kling, P. J.; Chang, R. S. L. *Life Sci.* **1987**, *39*, 1631.

Table II. Receptor Binding Affinities for 3-[(2-Indolylcarbonyl)amino]benzodiazepines[a]



compd	X	R_1	R_2	R_3	stereo.	IC_{50}, μM CCK pancreas	IC_{50}, μM CCK brain	IC_{50}, μM gastrin
9	H	H	H	H	*RS*	0.0047	8.0	4.0
43	F	H	H	H	*RS*	0.0021	3.0	4.6
44	F	CH_3	H	H	*RS*	0.0014	0.3	0.19
45	F	CH_3	CH_3	H	*RS*	0.0013	1.0	1.6
46	F	CH_2COOH	H	H	*RS*	0.0015	5.6	0.39
47	F	H	H	5′-F	*RS*	0.005	12.0	>10.0
48	F	H	H	5′-Cl	*RS*	0.071	38.0	20.0
49[b]	H[b]	H[b]	H[b]	H[b]	*RS*	13.0	33.0	>10.0
50	H	CH_3	H	H	*RS*	0.0008	0.8	0.72
51	H	CH_3	CH_3	H	*RS*	0.0014	15.0	2.0
52	H	CH_2COOH	H	H	*RS*	0.0014	6.0	0.65
53	F	H	H	5′-Br	*RS*	0.12	50.0	>10.0
54	F	H	H	5′-OH	*RS*	0.071	16.0	29.0
55	F	H	H	5′-OCH_3	*RS*	0.2	29.0	>10.0
56	F	H	CH_3	H	*RS*	0.0047	7.0	6.3
2	H	CH_3	H	H	*S*	0.00008[+]	0.27	0.17
57	H	CH_3	H	H	*R*	0.0083[+]	3.7	1.4
58	F	CH_3	H	H	*S*	0.0006	0.3	0.028
59	F	CH_3	H	H	*R*	0.019	1.1	0.24
60	F	CH_2COOEt	H	H	*RS*	0.003[+]	0.2	0.12

[a] Binding affinities defined as in Table I, footnote *a*. [b] This compound contains an *N*-methyl substituent on the exocyclic amide nitrogen.

pounds at one or more dose levels ($N \geq 10$/dose) by the oral route 1 h prior to CCK-8. CCK-8 (80 μg/kg, sc) was given 5 min prior to a charcoal meal and gastric emptying determined 5 min later. ED_{50} values were based upon data obtained with at least three dose levels by regression analysis. The data are presented in Table VI.

Discussion

On the basis of the good CCK-receptor affinities of benzodiazepines containing the 3-indolemethyl side chain,[4] the related indole-based amides **3–9** were synthesized for initial investigation of the 3-amido series. As the activity data in Table I show, these compounds proved active but undistinguished CCK antagonists with one notable exception, the 2-indolecarboxamide **9**. The latter compound demonstrated conspicuously higher potency for blockade of CCK-A receptors, with excellent selectivity vs gastrin and brain (CCK-B) receptors. Examination of a variety of additional amides revealed several comparably active leads (Table I) including such analogues of the 2-indolyl compound as **11**, **17**, and **34**, as well as a class of benzoyl derivatives represented by **12**. The 2-indolecarboxamide lead was examined in detail through the structures presented in Table II, and the benzoyl lead was investigated through the analogues in Table III.

The results in Tables I–III indicate that, compared to the 3-alkylbenzodiazepines described previously,[4] the 3-acylamino compounds provide ligands with substantially (100–1000×) greater affinities for the CCK-A receptor. The preferred configurations for CCK-A receptor affinity in the two classes are the same; that is, the preferred 3*S* configuration of the amides of Tables I–III has the same spatial orientation of the 3-substituent as does the preferred 3*R* arrangement in the alkyl compounds previously described.[4] The change from 3*R* in the alkyl series to 3*S* in the amides results from application of the Cahn, Ingold, Prelog nomenclature rules[17] used to derive these designations.

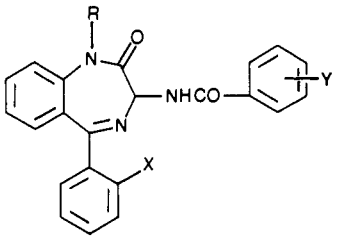
A detailed structural examination of a representative (acylamino)benzodiazepine CCK antagonist is afforded by the X-ray structure of **2**. The crystal contains two independent molecules of **2**, one of which is illustrated in Figure 1. These two molecules are very similar in ring structure and differ primarily in the orientation of the 3-(2-indolecarboxamide) substituent with respect to the benzodiazepine ring, as described in the Experimental Section. The benzodiazepine rings in these molecules are conformationally similar to those observed in 3-unsubstituted benzodiazepines. Hamor and Martin[18] have compared the X-ray structures of 20 previously reported benzodiazepines, using a list of nine key parameters to illustrate the close similarities among these compounds. The same parameters for the two molecules of compound **2** are listed in Table VII. When compared with the published values,[18] they illustrate that the benzodiazepine rings in **2** fit the norm established by those predecessors in every respect.

In each of the two molecules seen in the X-ray structure of **2**, the 3-substituent occupies a pseudo-equatorial position, again consistent with prior observations in the 3-methylbenzodiazepine series.[19] The indolecarboxamide groups in both molecules of **2** are fully planar (all dihedral angles 180 or 0 ± 5°) as expected.

A number of the analogues shown in Tables I–III (e.g., **2**, **12**, **17**, **34**, **50**, **93**, **95**, **104**, **112**, etc.) serve to illustrate

(17) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.
(18) Hamor, T. A.; Martin, I. L. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elsevier: New York, 1983; pp 193–205.
(19) Blount, J. F.; Fryer, R. I.; Gilman, N. W.; Todaro, L. J. *Mol. Pharmacol.* **1983**, *24*, 426.

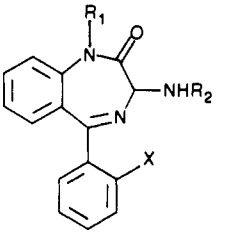
Table III. Receptor Binding Affinities for 3-(Benzoylamino)benzodiazepines[a]



					IC_{50}, μM		
					CCK		
compd	X	Y	R	stereo.	pancreas	brain	gastrin
61	F	*p*-NO_2	H	*RS*	0.110	>50	>10
12	F	*p*-Cl	H	*RS*	0.006	40	14
62	F	*p*-Cl	CH_3	*RS*	0.0023	3.4	2.9
63	F	*p*-Cl	CH_2COOEt	*RS*	0.11	1.9	0.69
64	H	*p*-Cl	CH_3	*RS*	0.0083	40	6.7
65	H	*p*-Cl	H	*RS*	0.041	>40	8.2
66	F	H	H	*RS*	0.151	>40	28
67	F	o-Cl	H	*RS*	5.5	>40	18
68	F	*p*-Cl	CH_2COOH	*RS*	0.032	21	8.2
69	H	o-Cl	H	*RS*	7.5	>40	52
70	H	*o*-Cl	CH_3	*S*	1.7	83	130
71	H	o-Cl	CH_3	*R*	11	22	7.5
72	F	*p*-CF_3	H	*RS*	0.015	40	9.5
73	F	*p*-CH_3	H	*RS*	0.021	14	5
74[b]	H[b]	o-Cl[b]	CH_3[b]	*RS*	58	100	>100
75	H	*o*-Cl	CH_3	*RS*	3.4	>100	30
76	H	*m*-Cl	H	*RS*	0.081	75	19
77	F	*p*-OCH_3	H	*RS*	0.096	>40	5.4
78	F	*p*-$N(CH_3)_2$	H	*RS*	0.27	>100	>100
79	F	3,4-di-OCH_3	H	*RS*	1.7	>40	>40
80	F	F_5	H	*RS*	>10	>40	>40
81	H	3,4-di-Cl	H	*RS*	0.029	>40	25
82	H	*p*-Br	CH_3	*R*	0.7	2.9	2.4
83	H	*p*-Br	CH_3	*S*	0.0029	1.6	0.8
84[c]	F[c]	*p*-Cl[c]	CH_3[c]	*RS*	0.066	18.0	2.4
85	F	*p*-Cl	CH_3	*S*	0.0025	2.9	0.8
86	F	*p*-Cl	CH_3	*R*	0.049	11	5.2
87	H	*p*-SCH_3	H	*RS*	0.22	23	8
88	H	*p*-F	H	*RS*	0.48	43	9.4
89	F	*p*-Cl	*p*-$ClC_6H_4(CO)$	*RS*	0.018	3.7	0.55
90	F	*m*-Br	CH_3	*S*	0.0035	3.5	0.75
91	H	*m*-SCF_3	H	*RS*	1.5	>100	>100
92	H	*p*-CF_3	H	*RS*	0.24	65	36
93	F	*p*-Br	CH_3	*S*	0.0008	4	0.68
94	F	*p*-*t*-Bu	CH_3	*S*	0.019	8	2.4
95	F	*p*-I	CH_3	*S*	0.0008	3	0.53
96	F	o-Br	CH_3	*S*	6.2	70	19
97	F	*p*-CN	CH_3	*S*	0.043	31	9
98	H	*p*-*n*-Pr	H	*RS*	3.6	12	80
99	H	*p*-Ph	H	*RS*	100	18	>100
100	H	*p*-*n*-C_5H_{11}	H	*RS*	27	8	>100
101	H	*p*-*t*-Bu	H	*RS*	1.4	100	40
102	H	3,5-di-Cl	H	*RS*	0.5	>100	180
103	H	*p*-OH	H	*RS*	1.8	100	31
104	F	*m*-I	CH_3	*S*	0.00075	1.7	0.39
105	H	*p*-CN	H	*RS*	0.73	>100	22
106	F	*m*-I	CH_3	*R*	0.015	2.4	2
107	F	o-I	CH_3	*R*	58	3.8	4.4
108	F	o-I	CH_3	*S*	0.8	45	11
109	F	o-Br	CH_3	*R*	9	5.9	5.8
110	F	*o*-Cl	CH_3	*R*	3.4	16	3.7
111	F	o-Cl	CH_2COOEt	*RS*	>30[+]	3.2	1.3
112	H	o-NH_2, *p*-Cl	CH_3	*RS*	0.0009[+]	2.4	1.9
113	H	*p*-*n*-C_5H_{11}	CH_3	*S*	0.25[+]	>100	>100
114	H	*p*-CF_3	CH_3	*S*	0.0013[+]	4.6	6.2
115	H	*p*-*n*-C_5H_{11}	CH_3	*R*	12[+]	>100	>100
116	H	*p*-CF_3	CH_3	*R*	115[+]	3.3	4.2
117	H	*p*-Br	CH_3	*RS*	0.001[+]	2.4	1.7
118	F	*p*-CF_3	CH_3	*RS*	0.02	1.8	1.8
119	F	*p*-CF_3	CH_3	*S*	0.011	1.4	0.44
120	F	*p*-*n*-C_5H_{11}	CH_3	*RS*	1.1	>100	>100
121	F	*p*-*n*-C_5H_{11}	CH_3	*S*	0.69	100	60
122	F	*p*-*t*-Bu	CH_3	*RS*	0.1	2.3	6.4
123	H	*o*-I	CH_3	*S*	1.1[+]	71	38

[a] Binding affinities defined as in Table I, footnote *a*. [b] This compound contains an *N*-methyl substituent on the exocyclic amide nitrogen. [c] This compound contains an *N*-oxide on the endocyclic nitrogen at the 4-position in the seven-membered ring.

Table IV. Receptor Binding Affinities for 3-Aminobenzodiazepines[a]



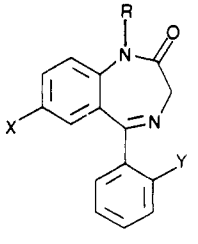
compd	X	R_1	stereo.	R_2	IC_{50}, μM: CCK pancreas	IC_{50}, μM: CCK brain	IC_{50}, μM: gastrin
124	H	H	*RS*	2-(3-indolyl)ethyl	3	100	>100
125	F	H	*RS*	2-indolylmethyl	0.087	100	>10
126[8,10]	H	H	*RS*	H	>100	>100	>100
127	F	H	*RS*	H	>100	>100	>100
128[10,11]	H	CH_3	*S*	H	100	>100	>100
129[10,11]	H	CH_3	*R*	H	>100	>100	>100
130	F	CH_3	*S*	H	57[+]	>100	>100

[a] Binding affinities defined as in Table I, footnote *a*.

that pancreatic (CCK-A) and brain (CCK-B) CCK receptors are distinguishable entities. These compounds show affinities 3 or 4 orders of magnitude higher for the CCK-A than for the CCK-B receptor. Similar selectivities for CCK-A vs guinea pig gastric gland gastrin receptors are also evident.

Selectivity in the opposite sense, that is for gastrin and CCK-B over CCK-A receptors, is observed in analogues such as **36**, **42**, **111**, and **116**, but potencies are only in the micromolar range. Higher gastrin/CCK-B receptor affinities are seen in other analogues (cf. **2**, **34**, **58**, **60**), but selectivity over CCK-A is not maintained. A potent, selective antagonist for gastrin and/or CCK-B receptors should be a useful pharmacological tool, but such an agent remains to be found in the 3-(acylamino)benzodiazepine series.

Several of the compounds reported here serve to reemphasize the distinction between the CCK-A and the brain benzodiazepine receptor also suggested by the earlier alkylbenzodiazepine compounds.[4] Consistent with previous reports,[20-23] we found "classical" benzodiazepines such as Diazepam (V, X = Cl, Y = H, R = CH_3), Flunitrazepam (V, X = NO_2, Y = F, R = CH_3), Clonazepam (V, X = NO_2, Y = Cl, R = H), and the compounds **131** (V, X = H, Y = H, R = CH_3)[13a] and **132** (V, X = H, Y = F, R = CH_3)[13a]



V

to have some affinity for the CCK-A receptor (Table VI), although only ca. 10^{-3}–10^{-6} times that for the brain benzodiazepine receptor. As the data in Table VI indicate, we have also found benzodiazepines of the present report to have a pronounced selectivity in the opposite sense, with very high affinities for the peripheral CCK receptor, 10^4 times that for the brain benzodiazepine receptor; the two receptors are apparently separate and distinct in their structural requirements for the bound ligand. A similar pattern of selectivities, of at least equal magnitude, is found between the CCK-B and brain benzodiazepine receptors. The very high selectivities of compounds such as **2** should permit exclusive blockade of CCK vs benzodiazepine receptors, perhaps facilitating clarification of the role of CCK in the action of anxiolytic benzodiazepines.

The effect of substitution on the compounds of Tables II and III is informative. Benzodiazepine ring substituents such as 2′-F and N^1-CH_3 provide compounds with equal or slightly enhanced affinity for the CCK-A receptor vs the corresponding unsubstituted entities (Tables I–III), just as was observed in the 3-alkyl series.[4] In the indolecarboxamide series (Table II), all substituents examined in the indole ring (**45**, **47**, **48**, **53–55**) were, with the exception of indole *N*-methyl (**45**) and possibly of 5′-F (**47**), detrimental to CCK receptor affinity. In the benzamide group (Table III), however, considerable variability in affinity was found, particularly among the many para-substituted compounds. CCK-A receptor affinity within this group showed an apparent correlation with the Hammett σ_p constants[24] for the individual para substituents.

Although the meta-substituted benzamides of Table III are smaller both in numbers (eight examples) and in substituent variety (75% halo), it does seem clear that *m*-halo compounds can achieve receptor affinities comparable to those of the corresponding para-substituted derivatives (cf. **76** vs **65**, **90** vs **93**, and **104** vs **95**), and that the stereochemical preference in the two series is the same (i.e., 3*S*: cf. **104** vs **106**).

In the equally limited ortho-substituted series, halo compounds constitute virtually the only class examined. Within this class, however, it appears safe to conclude that ortho-substitution, compared with para substitution, is detrimental to CCK-A receptor affinity (cf. **67** vs **12**, **69** vs **65**, **96** vs **93**, **108** vs **95**, **75** vs **64**, and **111** vs **63**). Indeed, comparison of compound **67** with **66** suggests the *o*-chloro

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substituent is a liability even vs no substituent. The stereochemical preference for 3S does still prevail in this series as well, however (cf. **70** vs **71** and **108** vs **107**).

That simple occupancy of this ortho position is not in itself responsible for the reduced receptor affinities of the ortho-substituted compounds is indicated by the *o*-amino-*p*-chloro analogue **112**, which, even in racemic form, rivals the best of the indoles and para-substituted benzamides in CCK-A receptor affinity. The *o*-aminophenyl ring might be expected to have an electron-rich aryl environment similar to that seen in the π-excessive indoles such as **2**. The effect of the ortho substituent in the benzamides of Table III, then, may be more electronic than steric. This is in accord with the apparent ability of the receptor to accommodate additional bulk in this region, as suggested by its tolerance of methyl substitution at the N^1 position of the indoles of Table II (**45** vs **44**, **51** vs **50**, **56** vs **43**).

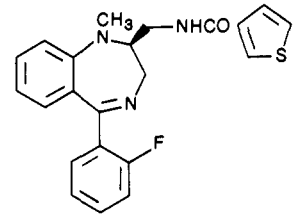
Across all pairs of enantiomers described in Tables I–III, the CCK-A receptor affinity ratio for the *R* vs the *S* enantiomer varies from a low of ca. 1.5 (**96**/**109**) to a high of 8000 (**114**/**116**), with most values clustering between 10 and 200. Explanations for this variation are not evident within the body of data presented here, and will most likely require detailed structural knowledge of the receptor for their adequate explanation.

Regardless of their mode of interaction with the CCK receptor, the best of the benzamides are CCK receptor ligands with very high affinities, comparable to that of the indole amide **2**. The affinities of these compounds for the CCK-A receptor approach and, in some cases, equal that of the minimum fully competent natural ligand CCK-8.[3] As indicated by the data in Table VI, these agents are also effective in vivo, serving as orally effective CCK antagonists with potential therapeutic utility. In general, the oral potencies of these compounds parallel their receptor affinities, spanning a range of ca. 50× in each case. In none of the compounds examined was any evidence of agonist activity observed.

Their similarity of receptor affinity not withstanding, the non-peptidal CCK antagonist benzodiazepines reported here represent a significant structural departure from the octapeptide CCK-8 (H-Asp-Tyr-(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2).[25] Attempts to explain the very high affinity of these benzodiazepines by their ability to mimic the peptide are hampered by the perennial difficulty of precisely defining and characterizing the biologically relevant conformation(s) for a peptide of this size. An experimental approach to this problem is to find fully potent yet conformationally constrained analogues of the peptide itself: such efforts are in progress.

Implicit in such studies, of course, is the assumption that the high receptor affinities of compounds such as **2** follow directly from their structural resemblance to the active conformer of the natural peptidal ligand: the closer the match, the higher the affinity. While such a "substrate match" provides perhaps the most straightforward explanation for these binding affinities, other models of ligand–receptor interaction cannot be ignored. An antagonist such as **2** might bind to the same site occupied by the natural ligand but using different binding determinants within this site. Alternatively, the antagonist may block the receptor site using binding elements both within and outside the binding site for the natural ligand. This concept of accessory binding sites is a recurring one in medicinal chemistry, having been invoked by Schaeffer,[26] by Humber and Voith,[27] and, in a particulary detailed presentation, by Ariens.[28] The extreme case wherein the antagonist and the natural ligand bind totally distinct sites, analogous to allosterism in enzyme inhibition, appears unlikely in view of the observed competitive nature of the CCK receptor binding of benzodiazepines such as *2*.[3,29]

Structural similarity between one of the benzodiazepines described here (**1**) and the natural peptide ligand CCK-7 (Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2) has been invoked[30] to support a "substrate match" mode of binding for compound **1** to the CCK receptor. However, no rigorous criterion for assessment of this "similarity" was presented, and in fact, the differences between **1** and the natural ligand CCK-7 seem more compelling than their similarities. Similarly, the most recent candidates for the natural ligands for the central (antianxiety) and peripheral benzodiazepine receptors, a peptide[31,32] and a porphyrin,[33] respectively, appear structurally quite different from the benzodiazepines which bind these same receptors. Another benzodiazepine, Tifluadom (**133**), shows high affinity for the opiate receptor,[34] the natural ligand for which is an apparently unrelated peptide. This same benzodiazepine (**133**) has also been reported to have significant affinity for the CCK-A receptor.[35] Thus, a single ring system, the



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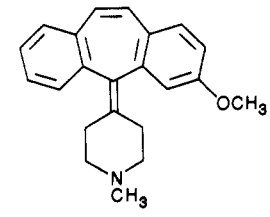

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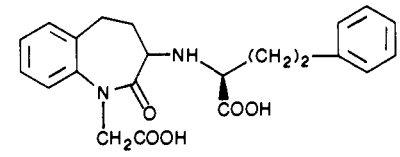

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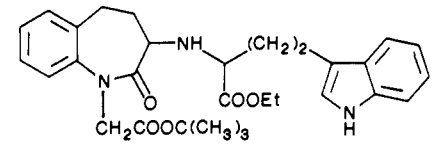

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Table V. Physical Data for Compounds of Tables I–IV

compd	formula	mp, °C	% purity HPLC	method	yield, %	MS molecular ion	anal.
2	$C_{25}H_{20}N_4O_2$	168–185	99.0	A/E	78	408	C, H, N
3	$C_{31}H_{31}N_5O_4$	173–177	63.7/36.0	B	16	(419) 537[a]	C, H, N
4	$C_{31}H_{31}N_5O_4$	171–174	68.9/29.5	B	78	(419)	C, H, N
5	$C_{24}H_{18}N_4O_2 \cdot 2.0CH_3OH$	265–268	99.7	B	20	394	C, H, N[c]
6	$C_{22}H_{20}N_4O_2$	264–265	93.1	A	34	408	C, H, N
7	$C_{26}H_{22}N_4O_2 \cdot 0.5H_2O$	176–182	99.7	B	30	422	C, H, N
8	$C_{27}H_{24}N_4O_2$	258–259	98.9	B	92	436	C, H, N
9	$C_{24}H_{18}N_4O_2 \cdot 0.2C_4H_{10}O$	265–268	99.2	A	51	394	C, H, N
10	$C_{25}H_{18}FN_3O_2S \cdot 0.1CHCl_3$	259–260	100	B	28	443	C, H, N
11	$C_{26}H_{20}FN_3O_2 \cdot 1.35H_2O$	219–222	98.3	B	70	425	C, H, N
12	$C_{22}H_{15}ClFN_3O_2 \cdot 0.2CHCl_3$	258–259	98.1	A	49	407	C, H, N
13	$C_{24}H_{16}FN_4O_2 \cdot 0.65H_2O$	109–111	91	B	37	424	C, H, N
14	$C_{23}H_{18}FN_3O_3 \cdot 0.28CHCl_3$	147–150	89.0	B	9	403	C, H, N
15	$C_{24}H_{18}FN_3O_2 \cdot 0.65H_2O$	255–257	95	A		399	C, H, N
16	$C_{23}H_{19}FN_4O_2 \cdot 0.55CHCl_3$	145–146	70	B	46	402	C, H, N
17	$C_{24}H_{16}FN_3O_3 \cdot 0.15CH_2Cl_2 \cdot 0.15C_4H_{10}O$	289–291	99.7	B	81	413	C, H, N
18	$C_{17}H_{14}FN_3O_2$	244–245	92		40	311	C, H, N
19	$C_{24}H_{20}N_4O_2 \cdot 0.45C_4H_8O_2$	252–272	96.0	B	24	396	C, H, N
20	$C_{30}H_{32}N_4O_4$	117–120	98.5	C	70	512	C, H, N
21	$C_{25}H_{24}N_4O_2$	92–108	98.8		100	412	C, H, N
22	$C_{25}H_{24}N_4O_2$	92–108	99.2		100	412	C, H, N
23	$C_{20}H_{15}FN_4O_2 \cdot 0.25C_4H_8O$	271–274	95.4	A	57	362	C, H, N
24	$C_{26}H_{19}N_3O_2$	287–294	100	A	58	405	C, H, N
25	$C_{20}H_{15}N_5O_2$	222–223	100	A	46	357	C, H, N
26	$C_{26}H_{19}N_3O_2$	162–167	96.5	A	41	405	C, H, N
27	$C_{21}H_{16}FN_3O_2S$	220–222	100	A	36	393	C, H, N
28	$C_{20}H_{14}FN_3O_2S \cdot 0.7H_2O$	238–239	98.8	A	44	379	C, H, N
29	$C_{29}H_{30}N_4O_4$	143–153	98.0	B	89	498	C, H, N
30	$C_{24}H_{22}N_4O_2 \cdot 0.1H_2O$	208–210	98.9			398	C, H, N
31	$C_{20}H_{21}N_3O_2 \cdot 0.2H_2O$	87–107	99.0	A	73	335	C, H, N
32	$C_{22}H_{25}N_3O_2$	83–102	99.0	A	70	349	C, H, N
33	$C_{23}H_{25}N_3O_2 \cdot 0.25H_2O$	212–214	98.9	A	45	375	C, H, N
34	$C_{25}H_{21}N_3O_2 \cdot 0.25H_2O$	126–140	94.6	A	64	395	C, H, N
35	$C_{21}H_{23}N_3O_2 \cdot 0.15C_5H_{10}O_2$	85–94	98.9	A	62	349	C, H, N
36	$C_{23}H_{25}N_3O_2$	212–214	100	A	49	376[b]	C, H, N
37	$C_{20}H_{19}N_3O_4$	184–186	98.6	A	36	366[b]	C, H, N
38	$C_{30}H_{31}FN_4O_4$	112–116	50.0/49.0	B	45	531[b]	C, H, N
39	$C_{30}H_{31}FN_4O_4$	108–116	98.6	B	45	531[b]	C, H, N
40	$C_{23}H_{18}ClN_3O_2 \cdot 0.4H_2O$	238–240	98.3	A	48	404[b]	C, H, N
41	$C_{25}H_{23}N_3O_3$	198–199	96.8	A	45	413	C, H, N
42	$C_{25}H_{23}N_3O_3$	198–199	98.7	A	45	413	C, H, N
43	$C_{24}H_{17}FN_4O_2 \cdot 0.16CH_2Cl_2$	290–291	97.0	A	65	412	C, H, N
44	$C_{25}H_{19}FN_4O_2 \cdot 0.75CH_2Cl_2 \cdot 0.5C_4H_{10}O$	282–284	96.8	C	30	426	C, H, N
45	$C_{26}H_{21}FN_4O_2 \cdot 0.75H_2O$	178–181	88.0	C	21	440	C, H, N
46	$C_{26}H_{19}FN_4O_4 \cdot C_3H_6O \cdot 0.8H_2O$	278	99.2		88	470	C, H, N
47	$C_{24}H_{16}F_2N_4O_2 \cdot 0.23CHCl_3$	268–271	91	A		430	C, H, N[d]
48	$C_{24}H_{16}ClFN_4O_2 \cdot 0.73CH_3OH$	275–279	87.8	A	10	446	C, H, N
49	$C_{25}H_{20}N_4O_2 \cdot 0.25H_2O$	287–288	97.2	A	52	408	C, H, N
50	$C_{25}H_{20}N_4O_2 \cdot 0.1C_4H_{10}O \cdot 0.15CH_2Cl_2$	269–270	98.2	C	50	408	C, H, N
51	$C_{26}H_{22}N_4O_2$	202–203	98.2	C	7	422	C, H, N
52	$C_{26}H_{20}N_4O_4 \cdot 0.3C_4H_{10}O \cdot 0.3CH_2Cl_2$	277–278	98.5		80	452	C, H, N
53	$C_{24}H_{16}BrFN_4O_2 \cdot 0.27CHCl_3$	181–183	81	A	16	490	C, H, N
54	$C_{24}H_{17}FN_4O_3 \cdot 0.2CHCl_3$	230 dec	86.7	B	51	428	C, H, N
55	$C_{25}H_{19}FN_4O_3 \cdot 0.26CHCl_3$	298–299	97.1	B	65	442	C, H, N[e]
56	$C_{25}H_{19}FN_4O_2 \cdot 0.13CHCl_3$	266–268	99.8	B		426	C, H, N
57	$C_{25}H_{20}N_4O_2 \cdot 0.1C_4H_{10}O$	165–183	98.0	A	76	408	C, H, N
58	$C_{25}H_{19}FN_4O_2 \cdot 0.2C_4H_{10}O$	162–187	99.6	A	78	426	C, H, N
59	$C_{25}H_{19}FN_4O_2 \cdot 0.1C_4H_{10}O$	162–187	99.6	A	78	426	C, H, N
60	$C_{28}H_{23}FN_4O_4 \cdot 0.1C_4H_{10}O$	100–160	96.7	C	90	498	C, H, N
61	$C_{22}H_{15}FN_4O_4 \cdot 0.1CHCl_3$	262–264	97.4	B	42	418	C, H, N
62	$C_{23}H_{17}ClFN_3O_2$	169–171	99.9	C	14	421	C, H, N
63	$C_{26}H_{21}ClFN_3O_4 \cdot 0.1C_4H_8O_2$	177–178	98.5	C	27	493	C, H, N
64	$C_{23}H_{18}ClN_3O_2$	214–220	98.0	C	42	403	C, H, N
65	$C_{22}H_{16}ClN_3O_2$	234–260	99.5	A	70	389	C, H, N
66	$C_{22}H_{16}FN_3O_2$	243–244	99.7		47	373	C, H, N
67	$C_{22}H_{15}ClFN_3O_2 \cdot 0.1C_4H_8O_2$	224	98.6		20	407	C, H, N
68	$C_{24}H_{17}ClFN_3O_4 \cdot 0.45NaI \cdot 0.75H_2O$	225–228	98.8	C	53	466[b]	C, H, N
69	$C_{22}H_{16}ClN_3O_2 \cdot 0.02CHCl_3$	232–234	98.2	A	90	389	C, H, N
70	$C_{23}H_{18}ClN_3O_2$	100–118	99.0	A	39	403	C, H, N
71	$C_{23}H_{18}ClN_3O_2$	102–120	98.6	A	56	403	C, H, N
72	$C_{23}H_{15}F_4N_3O_2 \cdot 0.2C_4H_8O_2$	209–211	97.8	A	64	441	C, H, N
73	$C_{23}H_{18}FN_3O_2 \cdot 0.4H_2O$	275–276	98.2	A	95	387	C, H, N
74	$C_{23.9}H_{19.8}ClN_3O_2 \cdot 0.35CHCl_3$	195–199	85/7	C		403 + 417	C, H, N
75	$C_{23}H_{18}ClN_3O_2 \cdot 0.55H_2O$	252–256	98.6	C	20	403	C, H, N
76	$C_{22}H_{16}ClN_3O_2 \cdot 0.5CHCl_3$	242–245	96.5	A	32	389	C, H, N
77	$C_{23}H_{18}FN_3O_3$	231–233	96.7	A	57	403	C, H, N

Table V (Continued)

compd	formula	mp, °C	% purity HPLC	method	yield, %	MS molecular ion	anal.
78	$C_{24}H_{21}FN_4O_2 \cdot 0.15H_2O$	256–258	97.6	A	39	416	C, H, N
79	$C_{24}H_{20}FN_3O_4 \cdot 0.13C_4H_{10}O \cdot 0.13CH_2Cl_2$	206–208	98.9	A	70	433	C, H, N
80	$C_{22}H_{11}F_6N_3O_2$	240–242	97.1	A	63	463	C, H, N
81	$C_{22}H_{15}Cl_2N_3O_2 \cdot 0.1CHCl_3$	260–263	100	B	90	423	C, H, N
82	$C_{23}H_{18}BrN_3O_2$	120–133	99.2	A	82	447	C, H, N
83	$C_{23}H_{18}BrN_3O_2$	120–133	99.1	A	73	447	C, H, N
84	$C_{23}H_{17}ClFN_3O_3 \cdot 0.05CHCl_3$	194–197	95.3		56	437	C, H, N
85	$C_{23}H_{17}ClFN_3O_2$	113–128	99.6	A	88	421	C, H, N
86	$C_{23}H_{17}ClFN_3O_2$	113–128	99.6	A	82	421	C, H, N
87	$C_{23}H_{19}N_3O_2S \cdot 0.65CHCl_3$	248–252	97.3	B	64	401	C, H, N
88	$C_{22}H_{16}FN_3O_2 \cdot 0.03CHCl_3$	241–245	95.3	A	39	373	C, H, N
89	$C_{29}H_{18}Cl_2FN_3O_3$	190–191	97.4	A	36	545	C, H, N
90	$C_{23}H_{17}BrFN_3O_2$	172–178	99.4	A	76	465	C, H, N
91	$C_{23}H_{16}F_3N_3O_2S$	230–232	98.6	B	55	455	C, H, N
92	$C_{23}H_{16}F_3N_3O_2$	257–259	99.5	A	29	423	C, H, N
93	$C_{23}H_{17}BrFN_3O_2$	123–135	100	A	61	465	C, H, N
94	$C_{27}H_{26}FN_3O_2$	184–190	100	A	38	443	C, H, N
95	$C_{23}H_{17}FIN_3O_2$	128–140	100	A	76	513	C, H, N
96	$C_{23}H_{17}BrFN_3O_2$	165–185	100	A	71	465	C, H, N
97	$C_{24}H_{17}FN_4O_2 \cdot 0.1C_4H_{10}O$	130–147	98.6	A	70	412	C, H, N
98	$C_{25}H_{23}N_3O_2$	158–162	100	A	45	397	C, H, N
99	$C_{28}H_{21}N_3O_2$	274–276	98.6	A	58	431	C, H, N
100	$C_{27}H_{27}N_3O_2$	203–205	99.5	A	50	425	C, H, N
101	$C_{26}H_{25}N_3O_2 \cdot 0.12CHCl_3$	259–261	94.0	A	52	411	C, H, N
102	$C_{22}H_{15}Cl_2N_3O_2$	258–260	95.5	B	52	423	C, H, N
103	$C_{22}H_{17}N_3O_3 \cdot 0.3H_2O$	227–230	95	B	10	371	C, H, N
104	$C_{23}H_{17}FIN_3O_2$	105–120	96.3	A	59	513	C, H, N
105	$C_{23}H_{16}N_4O_2 \cdot 0.05CHCl_3$	275–277	97.3	A	31	380	C, H, N
106	$C_{23}H_{17}FIN_3O_2$	169–172	97.5	A	55	513	C, H, N
107	$C_{23}H_{17}FIN_3O_2$	170–175	99.7	A	74	513	C, H, N
108	$C_{23}H_{17}FIN_3O_2$	169–172	98.4	A	75	513	C, H, N
109	$C_{23}H_{17}BrFN_3O_2$	155–160	99.4	A	74	465	C, H, N
110	$C_{23}H_{17}ClFN_3O_2$	157–165	99.0	A	57	421	C, H, N
111	$C_{26}H_{21}ClFN_3O_4 \cdot 0.35H_2O$	glass	97.2	C	25	493	C, H, N
112	$C_{23}H_{19}ClN_4O_2 \cdot H_2O$	146	100	D[g]	25	418	C, H, N
113	$C_{28}H_{29}N_3O_2$	76–82	99.7	A	42	439	C, H, N
114	$C_{24}H_{18}F_3N_3O_2 \cdot 0.25C_6H_{14}$	125–127	99.9	A	53	437	C, H, N
115	$C_{28}H_{29}N_3O_2 \cdot 0.25H_2O$	70–77	100	A	13	439	C, H, N
116	$C_{24}H_{18}F_3N_3O_2 \cdot 0.25C_6H_{14}$	124–130	99.2	A	42	437	C, H, N
117	$C_{23}H_{18}BrN_3O_2 \cdot 0.05C_3H_6O$	238–240	99.5	A	87	447	C, H, N
118	$C_{24}H_{17}F_4N_3O_2$	191–193	99.6	A	50	455	C, H, N
119	$C_{24}H_{17}F_4N_3O_2$	102–111	99.6	A	50	455	C, H, N
120	$C_{28}H_{28}FN_3O_2 \cdot 0.15H_2O$	76–82	99.1	A	45	457	C, H, N
121	$C_{28}H_{28}FN_3O_2$	70–77	98.0	A	38	457	C, H, N
122	$C_{27}H_{26}FN_3O_2$	191–193	98.7	A	60	443	C, H, N
123	$C_{23}H_{18}IN_3O_2 \cdot 0.3C_4H_8O_2$	115–120	99.6	A	84	496[b]	C, H, N
124	$C_{25}H_{22}N_4O \cdot 0.13CH_2Cl_2$	196–198	94.0		25	394	C, H, N
125	$C_{24}H_{19}FN_4O$	200–202	97.7		19	398	C, H, N
126	$C_{15}H_{13}N_3O \cdot 0.56H_2O$	201–202	93.2		32	251	C, H, N
127	$C_{15}H_{12}FN_3O \cdot 0.095CH_2Cl_2$				48		C, H, N[f]
128	$C_{16}H_{15}N_3O \cdot 0.15H_2O \cdot 0.15C_4H_{10}O$	55–72	97.6		58	265	C, H, N
129	$C_{16}H_{15}N_3O \cdot 0.20H_2O \cdot 0.15C_4H_{10}O$	55–72	96.7		72	265	C, H, N
130	$C_{16}H_{14}FN_3O$	gum	99.6		58	284[b]	C, H, N

[a] FABMS. [b] FABMS, M + H. [c] H: calcd, 5.72; found, 4.62. [d] N: calcd, 12.24; found, 11.66. [e] N: calcd, 11.83; found, 11.16. [f] N: calcd, 15.15; found, 14.55. [g] The amide was formed by mixed anhydride (isobutyl chloroformate) coupling between the 3-aminobenzodiazepine and 4-chloroanthranilic acid.

5-phenyl-1,4-benzodiazepine ring, provides ligands for a surprisingly diverse collection of receptors, the natural ligands for which appear to bear little resemblance to one another or to the benzodiazepines in question. The only obvious similarity is among the benzodiazepine structures themselves. These structures appear to contain common features which facilitate binding to various proteinaceous receptor surfaces, perhaps through binding elements different from those employed for binding of the natural ligands.

Nor are such multiple activities limited to the benzodiazepines. One enantiomer of the cyproheptadine derivative **134**, for example, is a peripheral anticholinergic, while the other shows antiserotonin, antihistaminic, and orexigenic activity.[36] Analogues of this compound are known which combine 10^{-8} M or higher affinities for dopamine, α-adrenergic, serotonin, and muscarinic cholinergic (but not benzodiazepine) receptors in a single agent.[37] Benzazepines such as **135** are effective ligands for the enzyme which cleaves the peptide angiotensin I,[38] while

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Table VI. Benzodiazepine, CCK, and Gastrin Receptor Binding Affinities and in Vivo CCK Antagonist Potencies for Selected Benzodiazepines

compd	IC_{50},[a] μM [^{125}I]CCK pancreas	[^{125}I]CCK brain	[^{125}I]gastrin: gastric glands	[^{3}H]benzodiazepine:[b] brain	IC_{50} CCK (pancreas)/IC_{50} BZD (brain)	CCK antagonism: in vivo ED_{50},[c] mg/kg, po
diazepam (V: X = Cl, Y = H, R = CH_3)	>100	>100		0.007	>10000	
clonazepam (V: X = NO_2, Y = Cl, R = H)	>100	>100		0.0017	>58000	
flunitrazepam (V: X = NO_2, Y = F, R = CH_3)	>100	>100		0.0017	>58000	
132[13a] (V: X = H, Y = F, R = CH_3)	42	>100	>100	0.024	1750	
131[13a] (V: X = H, Y = H, R = CH_3)	24.6	>100	94	0.065	378	
128	100	>100	>100	>100*		
129	>100	>100	>100	8.5*	>11	
1	3.4	>100	30	>100	<0.03	>300
9	0.0047	8.0	4.0	>100	<0.000 047	0.4
50	0.0008	0.8	0.72			0.08
51	0.0014	15.0	2.0	>100*	<0.000 014	1.9
2	0.00008+	0.27	0.17			0.04
57	0.0083+	3.7	1.4			0.4
52	0.0014	6.0	0.65			0.5
12	0.006	40	14			1.4
62	0.0023	3.4	2.9			0.2
83	0.0029	1.6	0.8	>100*	<0.000 01	0.4
82	0.7	2.9	2.4	15*	0.05	

[a] Binding affinities as defined in Table I, footnote *a*. [b] [^{3}H]Benzodizepine binding is IC_{50} (μM) for half maximal inhibition of binding of [^{3}H]diazepam or (*) [^{3}H]flunitrazepam in rat or guinea pig brain, respectively. [c] In vivo activities were determined as described under the Biology section.

Table VII. Geometrical Parameters Derived from X-ray Crystal Structure Analysis of Compound **2** (the Parameters Are As Defined by Hamor and Martin[18])

	Θ_1	Θ_2	Θ_3	Δ	*T*(N1–C2)	*L*(N1–C2)	*L*(C5–C24)[b]	*T*(C5–C24)[b]
2, molecule A[a]	58	39	62	8.4	−12.5[c]	1.36	1.52	−22,[c] 158
2, molecule B[a]	67	36	62	3.7	−5.8[c]	1.40	1.47	−41,[c] 141

[a] Molecules A and B are the two independent molecules observed in the X-ray of **2**. [b] *L*(C5–C24) and *T*(C5–C24) correspond to *L*(C5–C1′) and *T*(C5–C1′) of Hamor and Martin.[18] The difference is in the numbering scheme employed by these authors as compared with that seen in Figure 1. [c] The negative sign reflects the specific enantiomer seen in Figure 1.

the closely related **136** and its analogues are effective CCK-A receptor ligands.[39] Similar examples of a single molecular framework able to provide ligands for diverse receptors are discussed by Ariens.[28]

What are the implications of these observations for drug design? High specificity is a feature common to most biological receptors, so that seeking a "close" match to the structure of a natural ligand is a legitimate approach to the search for new drugs. As in the comparison of **1** and CCK-7 cited above,[30] however, there is frequently little rigor in the definition of "close". The 10^{-11} M binding constant of even a very potent receptor ligand such as **2** reflects but a modest 12–13-kcal increase in binding energy compared with an "inactive" compound (K_i = ca. 10^{-2} M). Such an energy increment represents the approximate contribution of just three or four well-placed hydrogen bonds or ca. 12 good van der Waals contacts.[40] Further, the energies of these most likely modes of binding, hydrogen bonding and van der Waals interactions, are high order functions of (i.e., very sensitive to changes in) interatomic distance[41] and, particularly for hydrogen bonds, of interatomic orientation as well.[40] Thus, the difference between a very well bound ligand and a very poorly bound one in terms of atomic positions and orientations may be quite small indeed: the entire range from excellent (e.g., K_i = 10^{-11} M) to poor (e.g., K_i = 10^{-2} M) ligand may be spanned by displacements of just a few atoms by only an angstrom or two from their ideal positions.

Against this background, the task of designing a novel structure with high affinity for a given receptor by model comparisons with a natural ligand becomes formidable. To detect a "close match" by the criterion of receptor binding requires the ability to discern total binding energy differences between structure and reference on the order of a single kilocalorie over the entire molecular array and for every factor of significance in binding. The results reported in this work illustrate only too clearly how small structural changes can make the difference between a well-bound ligand and a poorly bound one (see Table III), and how numerous subtle factors can dramatically influence this difference in ways difficult to explain even after the fact.

Compound **2** is an excellent CCK receptor ligand; compound **1** is a mediocre one. Yet, the similarities between the X-ray structures of these compounds appear much "closer" than between either compound and the peptide ligand CCK-7.[30] Highly potent compound **95** and its 50-fold less potent analogue **97** appear virtually indistinguishable upon model examinations, and the structure of the 10^{-5} M affinity CCK receptor ligand **49** offers little clue that it is but a single methyl group away from being the 10^{-9} M affinity compound **9**. These examples provide some indication of the level of rigor and sophistication with which structural similarity must be examined in designing new receptor ligands by modeling existing ones. Successful design of high-affinity ligands by modeling of the target receptor would presumably require similarly precise and detailed information regarding the structure of the receptor as well.

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If it is true that a modest number of rather ordinary interactions, properly positioned, can endow a given structure with very high affinity for a specific receptor, then numerous effective binding configurations for this receptor other than the one selected by Nature for the natural ligand should be accessible within the large manifold of synthetic organic molecules. This is particularly true given the chemist's freedom from the key constraint on Nature, namely that the structure of any three-dimensional array to be synthesized in the biological realm must be reducible to a one-dimensional code.[42] Peptide receptors should comprise no necessary exception to this rule since, by this reckoning, the preeminence of peptides in Nature derives not so much from any unique receptor binding properties as from their particular versatility as solutions to the one-dimensional coding problem. These different binding modes should provide useful alternatives in the search for new drug leads.

The arguments discussed above suggest that direct modeling based on a natural receptor ligand is an exacting task. Unfortunately, the alternate approach, seeking new structure types with different effective binding configurations, can be equally difficult to apply, and for much the same reason: it involves examining a large field of structural possibilities using the same close-up, high-sensitivity instrument, the binding assay. A tool for narrowing the number of possibilities is needed for effective application of this approach.

One such tool may be provided by the observations cited previously, i.e., that certain select structures are able to provide high affinity ligands for more than one type of receptor. The significance of these observations appears not to have been fully appreciated, perhaps because they appear to contradict the concepts of individuality and selectivity of receptors, predominant in most models of receptor function. Commonality of the type suggested by these observations finds little rationale among such models. It is true, according to recent findings, that many diverse receptors share a common linkage to the guanine nucleotide binding protein (G-protein) effector, that these receptors appear to have evolved from the same ancestral gene, and that they remain structurally related to this day, notably in the membrane-spanning region where ligand binding sites are thought to occur.[43] Whether or not the G-protein connection provides the explanation for the multiple receptor affinities of the structures described above, however, is unclear. The scope of these multiple activities appears to transcend the limits of even the broad class of G-protein linked receptors.

What is clear is that certain "privileged structures" are capable of providing useful ligands for more than one receptor and that judicious modification of such structures could be a viable alternative in the search for new receptor agonists and antagonists. The work reported here and the examples cited above illustrate the potential of such an approach.

Conclusion

This work complements and completes that presented in our earlier paper.[4] In that paper, we reported the design and synthesis of nonpeptidal antagonists for a peptide hormone, cholecystokinin (CCK). In this paper, we have described the elaboration of those moderately effective prototypes into a new series of highly potent, orally effective compounds suitable for evaluation as therapeutic agents. These new compounds have aided in clarification of the distinctions among CCK-A, CCK-B, gastrin, and central benzodiazepine receptors. They have also provided a glimpse at the subtlety and diversity of factors involved in ligand binding to CCK (and presumably other) receptors. Arguments have been constructed to suggest that structures with high affinity for a given receptor may be more numerous, but at the same time more difficult to pinpoint than has heretofore been appreciated. The development of the compounds described here has illustrated an approach to that end having potentially wider utility, selective modification of "privileged structures" known to have provided ligands for diverse receptors in the past.

Several of the agents described here, including L-364,718 (**2**)[44a-d,g-m] and L-365,031 (**117**)[44e-g] are finding use as pharmacological tools for examination of the physiological role of CCK. The potential of these compounds as therapeutic agents is currently being evaluated.

Experimental Section

Melting points (Thomas-Hoover melting point apparatus) are uncorrected. Spectra were obtained as follows: IR spectra on a Perkin-Elmer 237 spectrophotometer, EI mass spectra on a VG MM 7035 mass spectrometer, FAB mass spectra on a VG MM/ZAB-HF spectrometer, ^{1}H NMR spectra on a Varian XL-300 or Nicolet NT-360 spectrometer, with Me_4Si as internal standard. HPLC was carried out on a Hewlett-Packard Model 1084B liquid chromatograph using a Waters C-18 column (30 × 0.39 cm). Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of the theory unless noted otherwise. Analytical TLC was carried out on 250 μm, 5 × 20 cm silica gel plates (60 F-254, E. Merck) with ultraviolet light and/or phosphomolybdic acid for visualization.

Syntheses. Specific examples presented below illustrate general synthetic methods A–E cited in Table V. Other physical data are given in that table. In general, samples prepared for physical and biological studies were dried in high vacuum (5 μm) over P_2O_5 for 18 h at temperatures ranging from ambient to 110 °C, depending on the sample melting point. Despite these measures, many of the compounds remained solvated (Table V). Where analytical data have been presented for such solvates, the presence of all indicated solvents has been verified by NMR.

Method A. *N*-(2,3-Dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-1*H*-indole-2-carboxamide (9). 3(*R*,*S*)-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**126**)[8] (1.7 g, 6.77 mmol) was suspended in methylene chloride (30 mL) and treated with a 30-mL methylene chloride solution of indole-2-carbonyl chloride[45] (1.28 g, 7.1 mmol). The pH of the reaction was adusted to 9.5 with triethylamine (1.0 mL, 7.19 mmol) and the solution stirred 15 min. The reaction mixture was chroma-

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tographed on silica gel eluted with 25% ethyl acetate in CH_2Cl_2 and the solvent was evaporated. The residue was triturated with ether and evaporated to give **9** as a white solid (2.42 g): ^1H NMR ($CDCl_3$) δ 5.8 (1 H, d, J = 7 Hz, C-3 proton), 7.15–7.75 (15 H, m, aro, N^1H) 7.95 (1 H, br d, J = 7 Hz, amide NH), 9.15 (1 H, br s, indole NH).

Method B. *N*-(2,3-Dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-3-[(trifluoromethyl)thio]benzamide (91). 3(*R,S*)-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**126**)[8] (80 mg, 0.318 mmol), 3-(trifluoromethyl)thiobenzoic acid (70.7 mg, 0.318 mmol), 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDC, 61 mg, 0.318 mmol), and 1-hydroxybenzotriazole hydrate (HBT, 43 mg, 0.318 mmol) were combined in freshly degassed dimethylformamide (DMF, 3 mL) and stirred at room temperature. The pH of the solution was adjusted to 9.5 with triethylamine (0.080 mL, 0.575 mmol), and stirring was continued for 30 min. The mixture was evaporated in vacuo, treated with 10% Na_2CO_3 (aqueous, 20 mL), and extracted with EtOAc (2 × 30 mL). The combined extracts were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. Crystallization of the residue from EtOAc gave pure **91**: ^1H NMR ($CDCl_3$) δ 5.78 (1 *H*, d, J = 7 Hz, C-3 proton), 7.18–8.28 (12 H, m, aro), 7.93 (1 H, d, J = 7 Hz, amide NH), 8.21 (1 H, s, N^1H).

Method C/D. *N*-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-1*H*-indole-2-carboxamide (50). Compound **9** (0.64 g, 1.62 mmol) and sodium hydride (78.0 mg of a 50% suspension in mineral oil, 1.62 mmol) were stirred in 7 mL of dry, degassed dimethylformamide under nitrogen in an ice bath. After 30 min, iodomethane (0.10 mL, 1.62 mmol) was added in one portion and the mixture stirred 30 min in the cold. The solvent was removed in vacuo and the residue treated with water and extracted with methylene chloride (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel with 5% (v/v) diethyl ether in CH_2Cl_2. Evaporation of the product fractions and crystallization of the residue from CH_2Cl_2 diluted with ether gave **50**: ^1H NMR ($CDCl_3$) δ 3.53 (3 H, s, N^1CH_3), 5.75 (1 H, d, J = 7 Hz, C-3 proton), 7.13–7.73 (14 H, m, aro), 8.07 (1 H, d, J = 7 Hz, amide NH), 9.27 (1 H, br s, indole NH).

Method E. (3*S*)-(−)-*N*-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-1*H*-indole-2-carboxamide (2). 3(*S*)-Amino-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**128**)[10,11] (1.4 g, 5.28 mmol) was acylated with indole-2-carbonyl chloride (0.95 g, 5.28 mmol) as described in method A above. Chromatography on silica gel with 7% (v/v) diethyl ether in CH_2Cl_2 provided the product **2** as a white solid (83%) after trituration with ether ^1H NMR: ($CDCl_3$) δ 3.65 (3 H, s, NCH_3), 5.75 (1 H, d, J = 7 Hz, C-3 proton), 7.13–7.74 (14 H, m, aro), 8.05 (1 H, d, J = 7 Hz, amide NH), 9.25 (1 H, br s, indole NH).

X-ray Crystal Structure Analysis of 2. Suitable crystals of **2** ($C_{25}H_{20}N_4O_2$) for X-ray diffraction studies formed from isopropyl acetate with space group symmetry of $P2_1$ and cell constants of a = 15.370 (7) Å, b = 10.021 (3) Å, and c = 16.383 (9) Å and β = 95.38 (5) Å for Z = 4. A single molecule of isopropyl acetate was found in each asymmetric unit (vide infra) to give a calculated density of 1.215 g/cm.[3] Of the 3636 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 2576 were observed ($I > 3\sigma(I)$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[46] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.047. The absolute configuration was determined by X-ray diffraction experiments on an iodinated analogue.[10] The two independent molecules have similar conformations except for twists in the two side chains of the diazepine ring: the dihedral angle for C2–C3–N12–C13 is −167.7° while that for C2′–C3′–N12′–C13′ is −110.0°; the dihedral angle for N4–C5–C24–C25 is −19.4° while that for N4′–C5′–C24′–C25′ is −38.6°. Three intermolecular hydrogen bonds were noted: O14–N16′ 2.87 Å; N16–O14′ 2.78 Å; and O101–N12′ 2.98 Å. Tables containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 1 is a computer-generated perspective drawing of **2** from the final X-ray coordinates showing the correct absolute stereochemistry.

(46) The following library of crystallographic programs was used: MULTAN-80, P. Main, University of York, York, England (1980); SDP Plus V1.1, Y. Okaya and B. A. Frenz, B. A. Frenz and Associates, College Station, Texas (1984).

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Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **2** (8 pages). Ordering information is given on any current masthead page.