Synthesis and X-ray Crystallographic Analysis of Quinazolinone Cholecystokinin/Gastrin Receptor Ligands

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Compounds exemplified by 2-[2-(5-bromo-1*H*-indol-3-yl)ethyl]-3-[3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone (**3**, IC_{50} = 0.0093 μM using mouse brain membranes) represent a structurally novel series of non-peptide cholecystokinin B receptor ligands. Since asperlicin, a selective CCK-A receptor antagonist, may be regarded as a conformationally constrained 2-substituted-3-phenyl-4(3*H*)-quinazolinone, the progenitor of compound **3** (compound **2**, 2-[2-(1*H*-indol-3-yl)ethyl]-3-phenyl-4(3*H*)-quinazolinone) might therefore represent a conformationally flexible pharmacophore of the natural product. To probe possible conformational preferences for this class of receptor ligands, in particular the spatial relationship between the indole and quinazolinone rings, we prepared a series of analogues with methyl substituents on the ethylene bridge as well as congeners with different linkers. The X-ray crystal structure conformation for compound **22** (2-[2-(1*H*-indol-3-yl)ethyl]-3-]-3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone, IC_{50} = 0.026 μM) is extended with the two heteroaromatic rings adopting an antiperiplanar arrangement around the central σ bond of the ethane linker, whereas the solid-state conformation for a less active analogue **19** (2-[2-(1*H*-indol-3-yl)-1-methylethyl]-3-[3-(1-methylethoxyphenyl]-4(3*H*)-quinazolinone, IC_{50} = 9.1 μM) is folded with the two heteroaromatic systems adopting a synclinal orientation. However, MM2 force field calculations (MacroModel, v 3.0) suggest that the energy difference between the folded and extended conformation is small. Thus, other factors such as unfavorable steric interactions may account for the difference in receptor affinity. For derivatives with one to three methylene units separating the indole and quinazolinone rings, maximal receptor binding activity was found when the distance separating the two heteroaromatic systems is defined by an ethyl group. Introducing unsaturation into the ethylene bridge of compound **3** limited the conformational flexibility of the molecule and decreased its receptor affinity greater than 2 orders of magnitude.

Cholecystokinin (CCK) is distributed in various molecular forms throughout the peripheral and central nervous systems[1] and mediates a broad range of physiological responses by interacting with specific high-affinity binding sites.[2] The search for potent non-peptide ligands for these receptors has led to the development of selective antagonists for both CCK-A and CCK-B receptor subtypes that are remarkable in their structural diversity.[3] We recently reported a structurally novel series of potent quinazolinone CCK-B/gastrin receptor ligands derived from a substructure analysis of the natural product asperlicin (**1**).[4] Compound **2** (IC_{50} = 0.67 μM using mouse brain membranes) emerged from this analysis as the starting point for our optimization studies (Figure 1). By introducing substituents onto the pendant phenyl ring and indole nucleus, we identified 2-[2-(5-bromo-1*H*-indol-3-yl)ethyl]-3-[3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone (**3**, IC_{50} = 0.0093 μM) as the most potent member of this series.

Although a preliminary quantitative structure–activity relationship (QSAR) analysis suggested a correlation between pendant phenyl ring substituent size (molar refractivity) and receptor affinity for a subset of these compounds,[4] little is currently known about the topology of the CCK receptor. Consequently, rational drug design efforts have focused on known ligand structures as a means of elucidating potentially important receptor binding interactions. Molecular modeling[5] and ^{1}H NMR studies[6,7] of cyclic CCK peptides and peptide fragments have been used to identify low-energy conformations that may provide insight into the bioactive conformation of the endogenous ligand. With respect to non-peptide receptor ligands, models to define pharmacophoric groups common to structurally diverse series have primarily focused on glutamic acid (e.g. lorglumide) and benzodiazepine-based examples.[8-12] The tryptophan-derived antagonists (e.g.

(1) For a review, see: Hökfelt, T.; Cortés, R.; Schalling, M.; Ceccatelli, S.; Pelto-Huikko, M.; Persson, H.; Viller, M. J. Distribution Patterns of CCK and CCK mRNA in Some Neuronal and Non-Neuronal Tissues. *Neuropeptides* **1991**, *19* (Suppl), 31-43.

(2) For recent reviews, see: (a) Woodruff, G. N.; Hill, D. R.; Boden, P.; Pinnock, R.; Singh, L.; Hughes, J. Functional Role of Brain CCK Receptors. *Neuropeptides* **1991**, *19* (Suppl), 45-56. (b) Woodruff, G. N.; Hughes, J. Cholecystokinin Antagonists. *Annu. Rev. Pharmacol. Toxicol.* **1991**, *31*, 469-501. (c) Itoh, S.; Lal, H. Influences of Cholecystokinin and Analogues on Memory Processes. *Drug Dev. Res.* **1990**, *21*, 257-276.

(3) See, for example: (a) Kerwin, J. F., Jr. Further Developments in Cholecystokinin Antagonist Research. *Drugs Future* **1991**, *16*, 1111-1119. (b) Bock, M. G. *Development* of Non-Peptide Cholecystokinin Type B Receptor Antagonists. *Drugs Future* **1991**, *16*, 631-640. (c) Iversen, L. L.; Dourish, C. T.; Iversen, S. D. Cholecystokinin Receptors: Synthetic Antagonists with Selectivity for Receptor Subtypes and Possible Clinical Applications. *Biochem. Soc. Trans.* **1991**, *19*, 913-915. (d) Nadzan, A. M.; Kerwin, J. F., Jr. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: New York, 1991; Vol. 26, pp 191-200.

(4) Yu, M. J.; Thrasher, K. J.; McCowan, J. R.; Mason, N. R.; Mendelsohn, L. G. Quinazolinone Cholecystokinin-B Receptor Ligands. *J. Med. Chem.* **1991**, *34*, 1505-1508.

(5) Pincus, M. R.; Murphy, R. B.; Carty, R.; Chen, J. Structure–Activity Relationships in Peptide Pharmacology: The Role of Conformational Analysis Using the Chain-Buildup Procedure; Biologically Active Conformations of Cholecystokinin. *Neurol. Neurobiol.* **1988**, *47*, 105-115.

(6) Roy, P.; Charpentier, B.; Durieux, C.; Dor, A.; Roques, B. P. Conformational Behavior of Cyclic CCK-Related Peptides Determined by 400-MHz ^{1}H-NMR: Relationships with Affinity and Selectivity for Brain Receptors. *Biopolymers* **1989**, *28*, 69-79.

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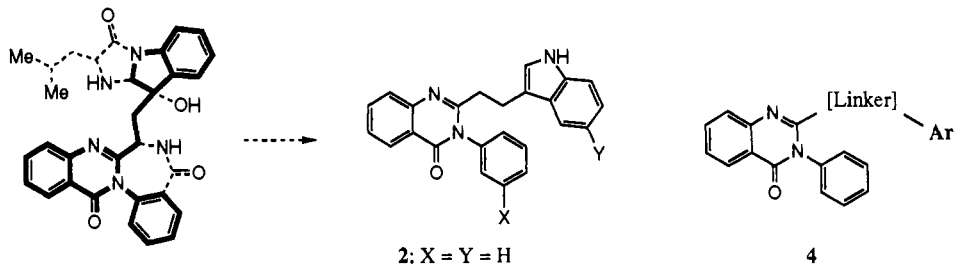

1: Asperlicin

2: X = Y = H
3: X = O-iPr, Y = Br

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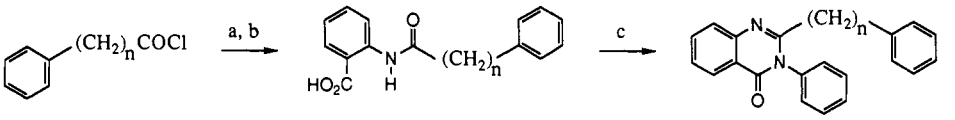
Figure 1. Possible substructure analysis of asperlicin with embedded 4(3*H*)-quinazolinone ring system highlighted.

Scheme I[a]

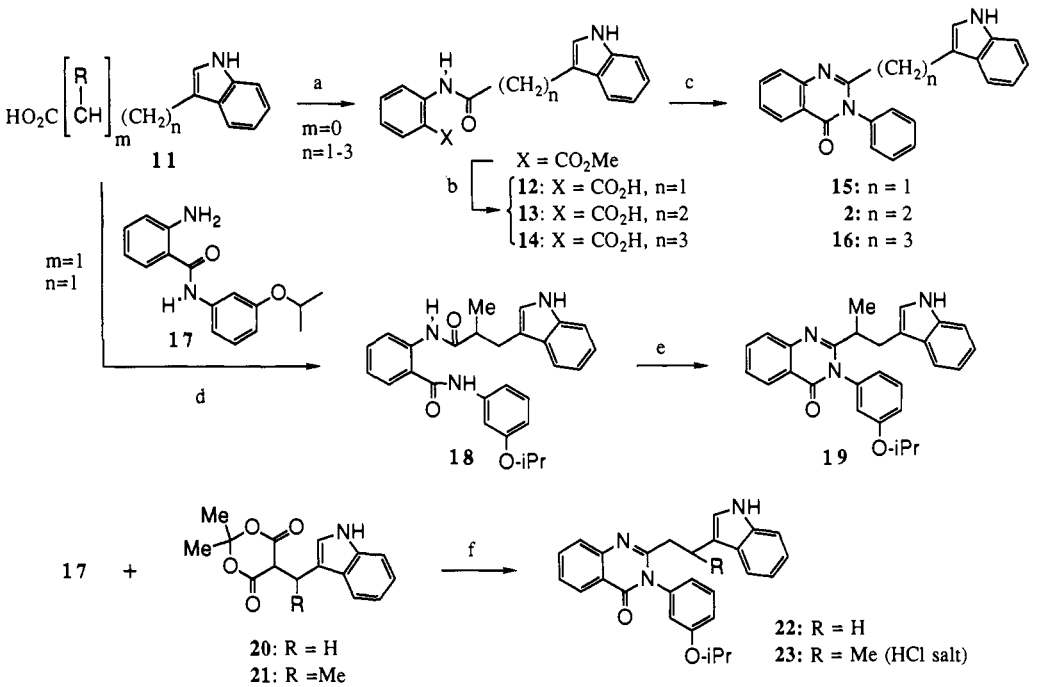


5: n = 1
6: n = 2
7: n = 3

8: n = 1 (HCl salt)
9: n = 2
10: n = 3 (HCl salt)

[a] (a) Methyl anthranilate; (b) NaOH; (c) PCl_3.

Scheme II[a]



[a] (a) Methyl anthranilate, 1,1'-carbonyldiimidazole, PPTs; (b) NaOH; (c) aniline, 1,1'-carbonyldiimidazole, PPTs; (d) 1,1'-carbonyldiimidazole; (e) PPTs; (f) 1,1'-carbonyldiimidazole, PPTs.

benzotript) have recently been included into this molecular construct to provide hybrid non-peptidal ligands of high affinity and selectivity for CCK-A receptors.[13] Although attempts to extend this approach in the design of glutamic acid derivatives with reversed receptor subtype selectivity have met with limited success,[11] structural modifications of lorglumide have been reported to yield CCK-B/gastrin selective agents.[14]

In connection with our classical SAR investigations of the quinazolinone series, we mapped the three-dimensional structure of representative examples from that study using a combination of X-ray crystallography and molecular modeling. To further define potentially important low-energy conformations for this class of compounds and to clarify the spatial relationship between the two hetero-

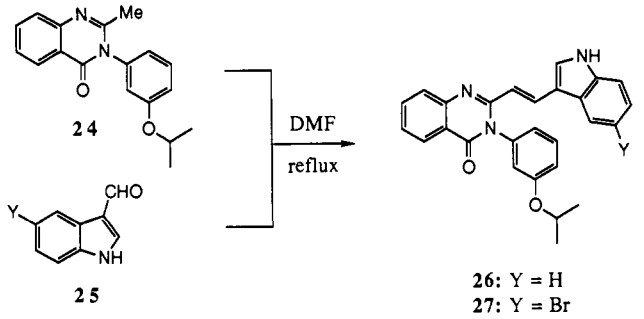
(11) Freidinger, R. M.; Whitter, W. L.; Gould, N. P.; Holloway, M. K.; Chang, R. S. L.; Lotti, V. J. Novel Glutamic Acid Derived Cholecystokinin Receptor Ligands. *J. Med. Chem.* **1990**, *33*, 591–595.

(12) van der Bent, A.; Blommaert, A. G. S.; Melman, C. T. M.; IJzerman, A. P., van Wijngaarden, I.; Soudijn, W. Hybrid Cholecystokinin-A Antagonists Based on Molecular Modeling of Lorglumide and L-364718. *J. Med. Chem.* **1992**, *35*, 1042–1049.

(13) Kerwin, J. F., Jr.; Wagenaar, F.; Kopecka, H.; Lin, C. W.; Miller, T.; Witte, D.; Stashko, M.; Nadzan, A. M. Cholecystokinin Antagonists: (*R*)-Tryptophan-Based Hybrid Antagonists of High Affnity and Selectivity for CCK-A Receptors. *J. Med. Chem.* **1991**, *34*, 3350–3359.

(14) Makovec, F.; Peris, W.; Revel, L.; Giovanetti, R.; Mennuni, L.; Rovati, L. C. Structure–Antigastrin Activity Relationships of New (*R*)-4-Benzamido-5-oxopentanoic Acid Derivatives. *J. Med. Chem.* **1992**, *35*, 28–38.

Scheme III



aromatic rings we also synthesized a series of structurally related congeners with (1) saturated linkers of different lengths, (2) an olefinic linker connecting the two heteroaromatic domains, and (3) a methyl group on the ethylene bridge.[15] We also prepared a number of analogues with a phenyl ring in place of the indole nucleus to assess the importance of the latter in receptor binding.

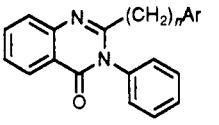
Chemistry

Several synthetic routes were examined for assembling the desired quinazolinones from their respective aniline, anthranilic acid, and indole component precursors. Compounds **8–10** which have a phenylalkyl substituent at C2 of the quinazolinone ring were prepared from the corresponding carboxylic acids **5–7** in the presence of aniline and phosphorous trichloride according to the procedure described by Grimmel et al. (Scheme I).[16] A parallel strategy was employed for preparing analogues **2**, **15**, and **16** beginning with methyl anthranilate and the indolecarboxylic acids represented by structure **11** ($m = 0$, $n = 1$–3, Scheme II). However, in contrast to the phenylalkyl derivatives, attempts to condense and cyclize the indole intermediates **12–14** with aniline using the phosphorous trichloride conditions provided only a complex mixture of products. As an alternative approach, the carboxylic acids were first activated with 1,1′-carbonyldiimidazole and then stirred with aniline and pyridinium *p*-toluenesulfonate (PPTS) in refluxing pyridine to provide the desired quinazolinones in modest but acceptable yields. In a related sequence, 2-methyl-3-(3-indolyl)propanoic acid[17] and 2-amino-*N*-(3-isopropoxyphenyl)benzamide (**17**) were similarly coupled and cyclized to afford the methyl congener **19**.

While this procedure furnished the desired final products, we were interested in a more general and convergent synthetic route that might allow a variety of simple substituted indoles to be incorporated directly into the synthesis without prior conversion to an indolepropionic acid. Toward that end indole, Meldrum's acid and an aldehyde (e.g. formaldehyde or acetaldehyde) were condensed according the procedure of Farlow et al. to provide conjugate addition products **20** and **21**.[18] These intermediates were then coupled with benzamide **17** in the presence of PPTS to furnish the targeted quinazolinones directly.[19] Since **20** and **21** were employed in the final coupling and cyclization reaction as a latent activated carboxylic acid, this sequence may represent another application of Meldrum's acid in heterocyclic synthesis.[20] Using this procedure, compounds **3**,[4] **22**, and **23** were prepared.

The olefinic derivatives **26** and **27** were prepared by stirring a mixture of the substituted 2-methyl-3-phenyl-4(3)-quinazolinone[21] **24** and indole-3-carboxaldehyde **25**

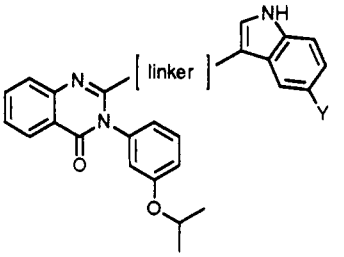
Table I. Effect of Tether Length on CCK-B Receptor Binding

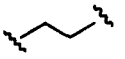
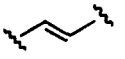
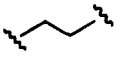
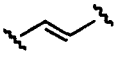
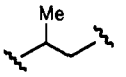
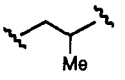


compd	n	Ar	CCK-B (IC_{50}, μM)[a]
8	1	phenyl	6%[b]
9	2	phenyl	27%[b]
10	3	phenyl	21%[b]
15	1	3-indole	36%[b]
2	2	3-indole	0.67 ± 0.15 ($n = 3$)
16	3	3-indole	20%[b]

[a] Inhibition of ^{125}I-CCK-8S binding to mouse brain membranes. [b] Percent inhibition of ^{125}I-CCK-8S binding to mouse brain membranes at test agent concentration of 10 μM.

Table II. CCK-B Receptor Binding Data



compd	linker	Y	CCK-B (IC_{50}, μM)[a]
22		H	0.026 ± 0.001 ($n = 5$)
26		H	0.43 ± 0.03 ($n = 3$)
3		Br	0.0093 ± 0.0015 ($n = 3$)
27		Br	1.4 ± 0.3 ($n = 3$)
19		H	9.1 ± 1.2 ($n = 4$)
23		H	0.070 ± 0.004 ($n = 3$)

[a] Inhibition of ^{125}I-CCK-8S binding to mouse brain membranes.

(15) A portion of this work has been presented previously. Yu, M. J.; McCowan, J. R.; Mason, N. R.; Deeter, J. B.; Jones, N. D.; Bruns, R. F.; Mendelsohn, L. G. Synthesis and Conformational Analysis of Alkyl Substituted Quinazolinone CCK-B/Gastrin Receptor Ligands. Presented at the 4th Chemical Congress of North America, New York, NY, August 25–30, 1991; MEDI 66.

(16) Grimmel, H. W.; Guenther, A.; Morgan, J. F. A New Synthesis of 4-Quinazolones. *J. Am. Chem. Soc.* **1946**, *68*, 542–543.

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(18) Farlow, D. S.; Flaugh, M. E.; Horvath, S. D.; Lavagnino, E. R.; Pranc, P. Two Efficient Syntheses of Indole-3-Propionic Esters and Acids. Further Applications of Meldrum's Acid. *Org. Prep. Proced. Int.* **1981**, *13*, 39–48.

(19) Yu, M. J.; Thrasher, K. J.; McCowan, J. R.; Mason, N. R.; Lucaites, V. L.; Gardner, A. J.; Bruns, R. F.; Mendelsohn, L. G. Design and Synthesis of Novel Selective Nonpeptide CCK-B Receptor Ligands. Presented at the 201st National Meeting of the Americal Chemical Society; Atlanta, GA, April 14–19, 1991; American Chemical Society: Washington, DC, 1991; MEDI 135.

(20) For a review on the synthesis, reactions and applications of Meldrum's acid in natural product synthesis, see: Bang-Chi, C. Meldrum's Acid in Organic Synthesis. *Heterocycles* **1991**, *32*, 529–597.

(21) Manhas, M. S.; Amin, S. G.; Rao, V. V. Heterocyclic Compounds; IX. A Facile Synthesis of Methaqualone and Analogs. *Synthesis* **1977**, 309–310.

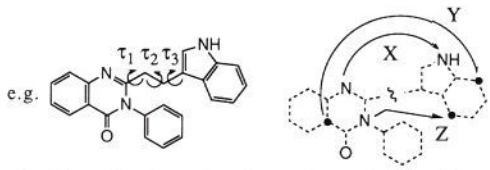


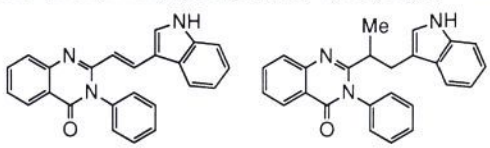
Figure 2. Example of torsional angel search using the MULTIC option of MacroModel for compounds **2**, **15**, **16**, and **28–30**. The indicated atomic distances (in Å) were calculated using the ANALYZ mode of MacroModel. Each energy-minimized conformer was then plotted on a three-dimensional graph (see Figures 3 and 4) using these distances as x, y, z coordinates.

in refluxing DMF according to the method of Gupton et al. (Scheme III).[22]

Results and Discussion

In Vitro Receptor Binding. CCK-B receptor binding was performed with mouse brain membranes according to a modified procedure of Chang and Lotti.[23] Table I summarizes the in vitro binding data for a series of unsubstituted indole and phenyl analogues with saturated alkyl linkers of different lengths (see generic structure **4**, Figure 1). Within the indole series of compounds, maximal receptor binding was observed when the two heteroaromatic domains were connected by an ethylene tether. All of the non-indole congeners examined (structure **4** where Ar = phenyl, substituted phenyl, naphthyl) as exemplified by compounds **8–10** were less active in the CCK-B receptor binding assay than **2**, the prototype for this series of non-peptide ligands. Unsaturation in the linker diminished receptor affinity from 1 to 2 orders of magnitude (e.g. **22** vs **26**, **3** vs **27**) but a methyl substituent on the ethylene bridge reduced receptor binding affinity only when placed on the carbon adjacent to the quinazolinone ring. Placing a methyl group adjacent to the indole ring had only a minor impact on receptor affinity (Table II).

Molecular Modeling. In parallel with our X-ray crystallographic investigation, we used molecular modeling to help distinguish possible differences in the families of minimized low-energy conformations for representative examples that lack an isopropoxyl substituent on the pendant phenyl ring (compounds **2**, **15**, **16**, and **28–30**).



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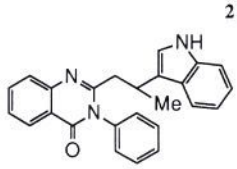

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Using MacroModel (v 3.0),[24] the starting structures were generated[25] and their energies were fully minimized using MM2 force field parameters. An exhaustive conformational search systematically varying (60° increments) all torsional angles t_1–t_{n+1} (n = number of carbons in the tether) in the tether as illustrated in Figure 2 was then performed. Each structure was subsequently optimized using the batch minimizer on a CRAY-2 with an energy limit of 4.8 kcal/mol above the global energy minimum. Using the atomic distances (in angstroms) defined in Figure 2, the resulting family of energy-minimized structures was plotted for all conformations within 2 kcal/mol of the global energy minimum conformation for each compound (Figures 3 and 4).

As summarized in Table I, affinity of the quinazolinone ligands for the CCK-B receptor is highly sensitive to the

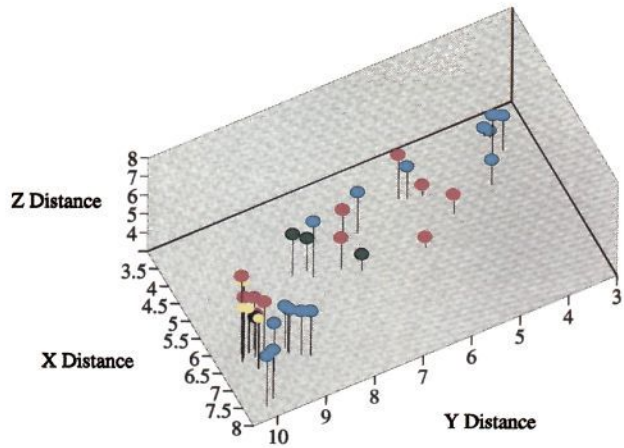

Figure 3. Family of energy-minimized conformations within 2 kcal/mol of the global energy minimum calculated by MacroModel (v 3.0) for compounds **2** (red), **15** (green), **16** (blue), and **28** (yellow) whose x, y, z coordinates are defined in Figure 2. The X-ray crystal structure conformation for compound **2** is represented by a black circle (x = 6.457, y = 9.785, z = 5.175).

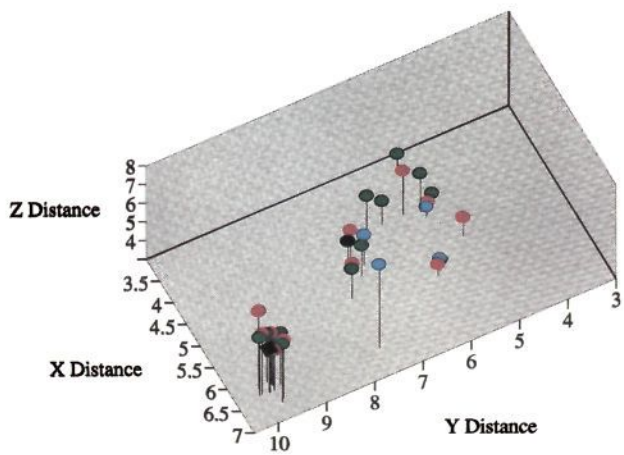

Figure 4. Family of energy-minimized conformations within 2 kcal/mol of the global energy minimum calculated by MacroModel (v 3.0) for compounds **2** (red), **29** (blue), and **30** (green) whose x, y, z coordinates are defined in Figure 2. The X-ray crystal structure conformation for compounds **19** (x = 4.808, y = 7.328, z = 4.677) and **22** (x = 6.388, y = 9.834, z = 5.301) is represented by a black circle and a black square, respectively.

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(25) The starting structures were drawn using the INPUT and DRAW modes of MacroModel. X-ray Structures were not used.

Table III. Crystal Data for Compounds 2, 19, and 22[a]

	2	19	22
formula	$C_{25}H_{23}N_3O_2$	$C_{28}H_{27}N_3O_2$	$C_{27}H_{25}N_3O_2$
formula wt	397.5	437.5	423.5
a, Å	10.302 (2)	12.168 (2)	19.939 (3)
b, Å	12.779 (3)	13.033 (2)	5.7760 (10)
c, Å	16.506 (3)	15.184 (3)	21.503 (3)
β, deg	106.21 (3)		113.330 (10)
V, Å^3	2086.6 (7)	2407.9 (7)	2273.9 (5)
Z	4		4
d_{calcd}, g/cm^3	1.265	1.207	1.237
reflections measd	2841	1887	3104
obsd reflections	1895	1703	2736
final R	0.066	0.05	0.056

[a] Reflections with 2θ less than 116.0° were measured on a Siemens R3m/V automated four-circle diffractometer using monochromatic copper radiation (λ = 1.541 78 Å). The structure was solved by direct methods using the Siemens SHELXTL PLUS (VMS) system and refined by the full-matrix least-squares method with anisotropic temperature factors for all atoms except hydrogen, which were included at calculated positions with isotropic temperature factors.

length of the tether connecting the indole and quinazolinone rings and is optimal when the distance is defined by an ethyl group. From MacroModel MM2 calculations, a region of conformational space (Figure 3, x = 6.0–6.6 Å; y = 9.5–10.0 Å) corresponding to the X-ray crystal structure conformation is accessible only to analogues with an ethyl tether (e.g. **2**). However, this region is also accessible to olefinic congener **28**. Since the unsaturated analogues exhibit a substantially reduced affinity for the receptor relative to their saturated counterparts (e.g. **22** vs **26** and **3** vs **27**), either electronic factors may significantly alter receptor binding by these compounds or this region of conformational space may not represent the bioactive conformation.

The calculated global energy minimum conformations for compounds **2** and **30** are predicted to have the two heteroaromatic rings extended from one another in an antiperiplanar arrangement around the central σ bond of the ethane linker. The global energy minimum conformation for **29**, on the other hand, is predicted to be folded with the two heteroaromatic rings adopting a synclinal orientation. Since the corresponding methyl-substituted analogue **19** is greater than 100-fold less active at blocking the CCK-B receptor relative to its structural isomer **23** or compound **22** (Table II), it is possible that an extended antiperiplanar arrangement of these two aromatic domains may more closely resemble the desired bioactive conformation. However, both an extended and folded conformation calculated to be less than 2 kcal/mol above the global energy minimum is accessible to both compounds **29** and **2**, respectively (Figure 4), suggesting that additional factors such as unfavorable steric interactions between the receptor and the ligand C26 methyl group (for atomic numbering see Figure 10) may contribute to the observed difference in receptor binding activity.

X-ray Crystallography. Compound **2** crystallized from methanol as colorless rods in the monoclinic space group $P2_1/c$ with unit cell dimensions summarized in Table III. A total of 2841 reflections with 2θ less than 116.0° were measured and the structure was solved by direct methods. Full-matrix least-squares refinement was conducted with anisotropic temperature factors for all atoms except hydrogen, which were included at calculated positions with isotropic temperature factors. A final residual index of 0.066 was obtained for 1895 observed reflections and no significant features on the final difference Fourier map were noted (largest difference peak and hole was 0.23 and −0.38 e Å^{-3}, respectively).

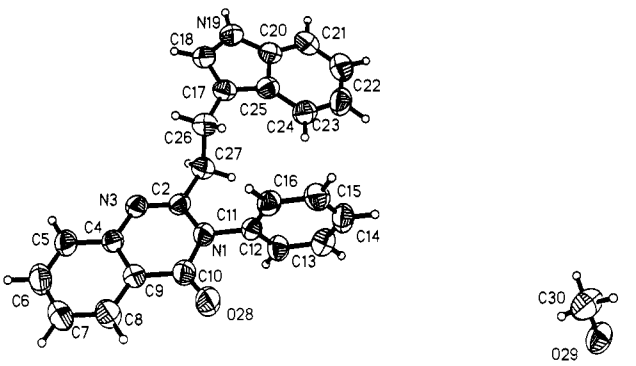

Figure 5. Computer-generated ORTEP plot of compound **2** with crystallographic numbering system. There is one molecule of methanol (crystallization solvent) in each asymmetric unit.

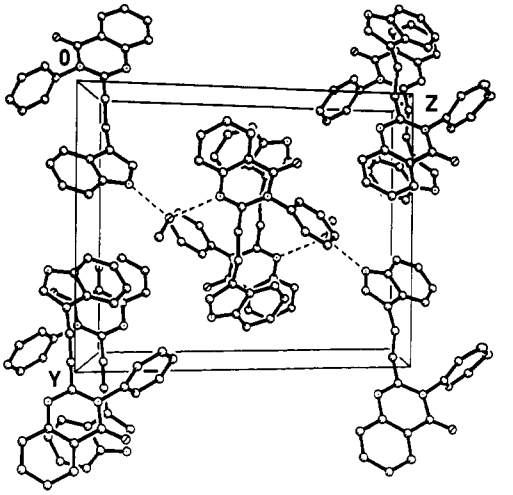

Figure 6. Unit cell contents and molecular packing of compound **2**. Dashed lines indicate possible intermolecular hydrogen bonds.

Compound **19** crystallized as colorless rods from methanol in the orthorhombic space group $P2_12_12_1$ with unit cell dimensions summarized in Table III. A total of 1887 reflections were measured and the structure was solved and refined as described above. The final R factor was 0.05 for 1703 observed reflections and no significant features on the final difference Fourier map were noted (largest difference peak and hole was 0.17 and −0.20 e Å^{-3}, respectively).

Compound **22** crystallized as colorless rods from methanol in the monoclinic space group $P2_1/n$ with unit cell dimensions summarized in Table III. A total of 3104 reflections were measured, and the structure was solved and refined as described above. The final R factor was 0.056 for 2736 observed reflections and again no significant features on the final difference Fourier map were noted (largest difference peak and hole was 0.20 and −0.39 e Å^{-3}, respectively). Final atomic coordinates and thermal parameters for all three structures are available as supplementary material.

Compound **23** was isolated as its free base and crystallized from methanol. However, the crystals were easily fractured and not of sufficient quality for X-ray analysis. After screening a variety of solvents, small colorless rods were finally obtained from ethanol. A single crystal was mounted in a capillary containing a small amount of the mother liquors, and X-ray data was collected as described above. Unfortunately, to date we have not been able to solve the structure by direct methods.

Figure 5 shows an ORTEP plot of compound **2** and the non-hydrogen crystallographic numbering system. Each unit cell contains 4 formula units, and as illustrated in

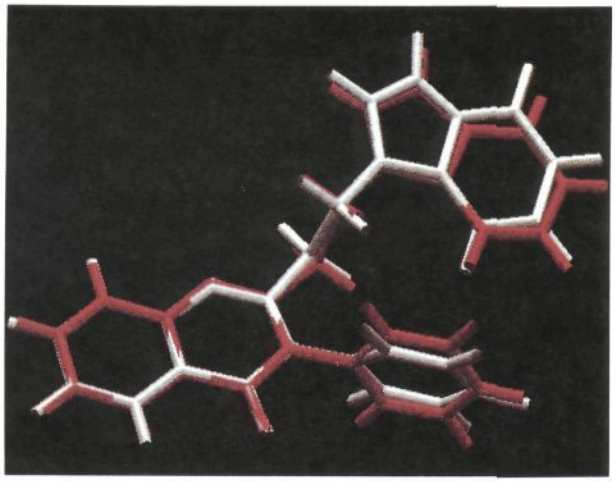

Figure 7. Global energy minimum conformation calculated by MacroModel for compound **2** (white) superimposed on the X-ray crystal structure (red). The molecule of methanol in the crystal structure was removed for clarity.

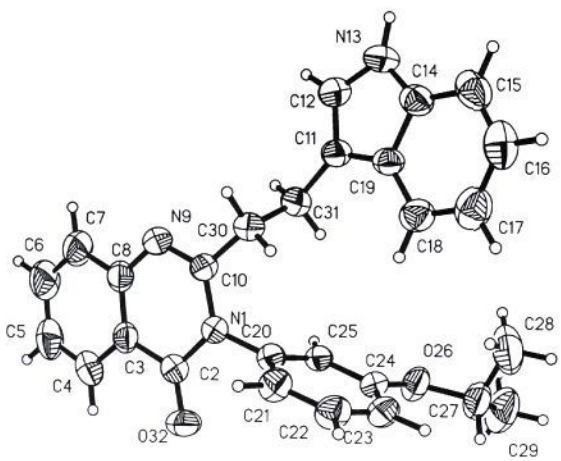

Figure 8. Computer-generated ORTEP plot of compound **22** with crystallographic numbering system.

Figure 6, the molecules are stacked in a head to tail fashion. A molecule of methanol, the crystallization solvent, is present in each asymmetric unit and is within hydrogen-bonding distance[26] to either an indole or quinazolinone nitrogen atom. The plane of the pendant phenyl ring is nearly orthogonal to that of the quinazolinone, and this appears to be a feature common to all three X-ray structures. In a global perspective, the molecule is extended with the two heteroaromatic systems adopting an antiperiplanar orientation around the C26–C27 σ bond (−175.6° for the dihedral angle defined by C17–C26–C27–C2). This crystal structure conformation corresponds well with the global energy minimum conformation predicted by the MacroModel torsional angle search and MM2 force field calculations described above (Figure 7).

Figure 8 shows an ORTEP plot of compound **22**. Although in this case no solvent was incorporated into the crystal lattice, the X-ray structures for compounds **2** and **22** are nearly identical, indicating that an isopropoxyl substituent in the meta position of the pendant phenyl ring does not significantly alter the overall conformation of the molecule

(26) Possible intermolecular hydrogen bonds (dashed lines in Figures 6 and 9) are noted when the distance (angstroms) between atoms is less than or equal to $1.6 + R_1 + R_2$, where R_1 and R_2 represent atomic radii.

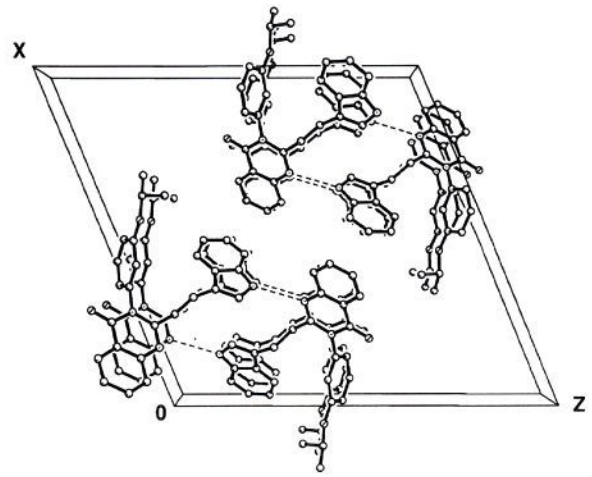

Figure 9. Unit cell contents and molecular packing of compound **22**. Dashed lines indicate possible intermolecular hydrogen bonds.

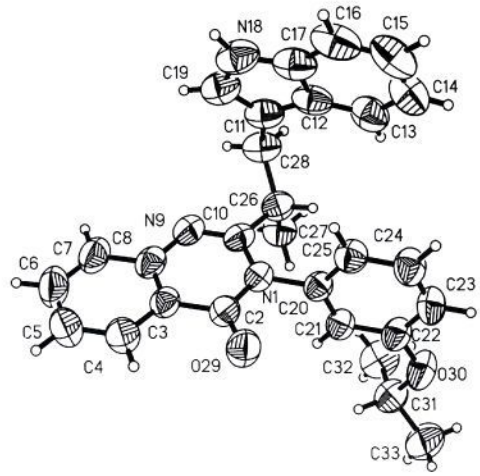

Figure 10. Computer-generated ORTEP plot of compound **19** with crystallographic numbering system. Although **19** is a racemic mixture, only one enantiomer is shown.

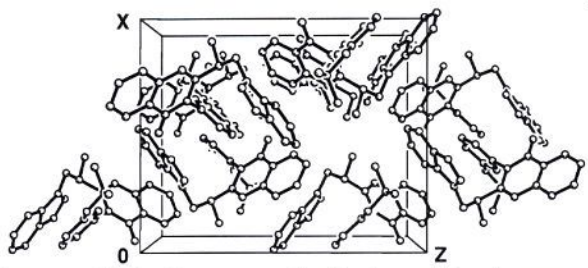

Figure 11. Unit cell contents and molecular packing of compound **19**.

(171.7° for the dihedral angle defined by C10–C30–C31–C11). However, in contrast to the crystal structure of compound **2**, molecules of this derivative are juxtaposed with possible intermolecular hydrogen bonds connecting the indole and quinazolinone nitrogen atoms of two paired molecules (Figure 9).

Figures 10 and 11 depict an ORTEP plot, the unit cell contents, and molecular packing for compound **19**. In contrast to **22**, the methyl congener exists in a folded conformation with the two heteroaromatic systems adopting a synclinal orientation around the C26–C28 bond of the ethane linker (66.2° for the dihedral angle defined by C10–C26–C28–C11). This conformation corresponds reasonably well with the global energy minimum confor-

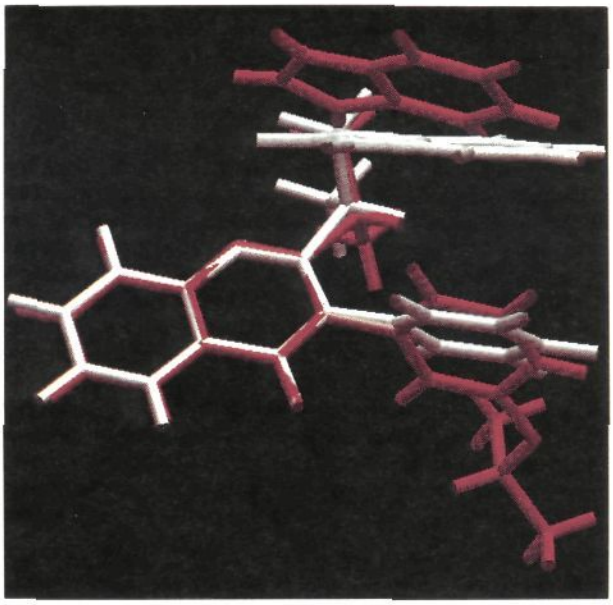

Figure 12. Global energy minimum conformation calculated by MacroModel for compound **29** (white) superimposed on the X-ray structure of **19** (red).

mation predicted for model system **29** (Figure 12). We have previously shown that a meta isopropoxyl group is optimal for in vitro binding to CCK-B receptors in mouse brain membrane and presumably occupies a lipophilic pocket with defined dimensions.[4] Increasing the size of this substituent to a cyclopentyloxyl group diminished receptor binding activity. In the crystal structures of **19** and **22**, the relative orientation of the isopropoxyl groups are similar (5.6° for the dihedral angle defined by C21–C22–O30–C31 of **19** and −12.7° for the dihedral angle defined by C23–C24–O26–C27 of **22**).

Conclusion. The quinazolinone representatives described in this study add to the benzodiazepine[27-29] and glutamic acid-based[14] CCK antagonists for which crystallographic structures have been reported. Although the benzodiazepine and quinazolinone heterocyclic nuclei differ structurally, they are related on the basis of atom pair descriptors.[30] Interestingly asperlicin (**1**), a selective CCK-A receptor antagonist, contains structural elements common to both series of non-peptide ligands and may be regarded as a conformationally constrained 2-substituted-3-phenyl-4(3H)-quinazolinone (Figure 1).[31] In that sense, compound **2** might therefore represent a conformationally flexible pharmacophore of the natural product but with reversed receptor subtype selectivity.[32] Reducing the conformational flexibility of the ethylene tether by introducing unsaturation diminished receptor binding affinity for two representative examples. While placing a methyl group onto the tether dramatically altered the crystal structure conformation of compound **19** relative to **2** (or **22**), MM2 force field calculations (MacroModel, v 3.0) suggest that the energy difference between the folded and extended conformation is small. Thus, substituents on the ethylene tether may influence receptor binding by creating unfavorable steric interactions with the receptor rather than by inducing changes in ligand conformation. Since the indole and quinazolinone (N4) nitrogen atoms may participate in intermolecular hydrogen bonding in the crystalline state, these atoms may represent important sites for CCK-B receptor binding interactions. Consistent with this hypothesis, derivatives with a phenyl ring in place of the indole nucleus exhibited lower receptor binding activity.

Experimental Section

Methods. Melting points were detemined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded with a GE QE-300 and were consistent with the assigned structure. Mass spectra were recorded with a CEC 21-110 (EI) or with a Varian-MAT 731 (FD) spectrometer. Microanalytical data were provided by the Physical Chemistry Department of Lilly Research Laboratories. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

X-ray Crystallography. Reflections with 2θ less than 116.0° were measured on a Siemens R3m/V automated four-circle diffractometer using monochromatic copper radiation (λ = 1.54178 Å). The structure was solved by direct methods using the routine SOLV of the Siemens SHELXTL PLUS[33] (VMS) system and refined by the full-matrix least-squares method with anisotropic temperature factors for all atoms except hydrogen, which were included at calculated positions with isotropic temperature factors. Final atomic coordinates and thermal parameters for all three structures are available as supplementary material.

2-(Phenylmethyl)-3-phenyl-4(3*H*)-quinazolinone Hydrochloride (8). Neat phenylacetyl chloride (15.3 g, 99.2 mmol) was added to a solution of methyl anthranilate (15.0 g, 99.2 mmol), pyridine (8.9 mL, 109 mmol), and CH_2Cl_2 (100 mL) at a rate sufficient to maintain gentle reflux. The mixture was stirred for 30 min under a Drierite drying tube, quenched with H_2O, and then acidified with 1 N HCl. The organic layer was separated and washed with 1 N NaOH, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting ester was saponified with 5 N NaOH (22 mL) in refluxing MeOH (100 mL). After 30 min, the mixture was cooled and concentrated in vacuo. The residue was acidified with 6 N HCl (30 mL), additional H_2O was added, and the precipitated solid was collected by suction filtration, washed thoroughly with H_2O, and dried in a vacuum oven at 60 °C to provide 25.0 g of **5** as a white solid, mp 187–189 °C. Anal. ($C_{15}H_{13}NO_3$) C, H, N.

A solution of PCl_3 (2.04 g, 14.9 mmol) in toluene (10 mL) was added dropwise to a suspension of the above acid (11.39 g, 44.6 mmol) in toluene (75 mL) at room temperature under N_2. The resulting mixture was stirred at reflux for 2 h, allowed to cool, and then quenched by first adding 10% aqueous Na_2CO_3 (100 mL) and then stirring vigorously for 10 min. The volatiles were removed in vacuo, and the aqueous residue was extracted with EtOAc. The organic layer was washed with NaOH, brine, dried

(27) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Friedinger, 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.; King, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. Design of Nonpeptidal Ligands for a Peptide Receptor: Cholecystokinin Antagonists. *J. Med. Chem.* **1987**, *30*, 1229–1239.

(28) 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. Methods for Drug Discovery: Development of Potent, Selective, Orally Effective Cholecystokinin Antagonists. *J. Med. Chem.* **1988**, *31*, 2235–2246.

(29) Liesch, J. M.; Hensens, O. D.; Springer, J. P.; Chang, R. S. L.; Lotti, V. J. Asperlicin, a Novel Nonpeptidal Cholecystokinin Antagonist from Aspergillus alliaceus. Structure Elucidation. *J. Antibiot.* **1985**, *38*, 1638–1641.

(30) Sheridan, R. P.; Venkataraghavan, R. New Methods in Computer-Aided Drug Design. *Acc. Chem. Res.* **1987**, *20*, 322–329.

(31) For an X-ray structure of asperlicin, see ref 29.

(32) Superimposing X-ray structures of our compounds with that of asperlicin may help further define differences and similarities in quinazolinone CCK-B receptor ligand conformation. However, although the crystal structure of the natural product is reported in the literature, to our knowledge atomic coordinates have not been published or deposited in the Cambridge Structural Database (v 3.10, January 1992).

(33) Sheldrick, G. M. *Shelxtl*, Rev 4, Instrument Corporation, 1983.

over Na_2SO_4, and concentrated under reduced pressure to afford a yellow oil. Crystallization from EtOAc/hexanes furnished 7.33 g of crude 8 free base as a white powder that was not sufficiently pure for testing. HCl gas was passed over the mother liquors from the above crystallization and the precipitated salt was collected by suction filtration. Recrystallization from MeOH/*i*-PrOH provided 1.50 g of 8 as a white solid, mp 208–211 °C. Anal. ($C_{21}H_{17}N_2OCl$) C, H, N.

2-(2-Phenylethyl)-3-phenyl-4(3*H*)-quinazolinone (9). Neat hydrocinnamoyl chloride (16.7 g, 99.2 mmol) was added to a solution of methyl anthranilate (15.0 g, 99.2 mmol), pyridine (8.9 mL, 109 mmol), and CH_2Cl_2 (100 mL) at a rate sufficient to maintain gentle reflux. The mixture was stirred for 30 min under a Drierite drying tube, quenched with H_2O, and then acidified with 1 N HCl. The organic layer was separated and washed with 1 N NaOH, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting ester was saponified with 5 N NaOH (22 mL) in refluxing MeOH (100 mL). After 30 min, the mixture was cooled and concentrated in vacuo. The residue was acidified with 6 N HCl (25 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to furnish 25.7 g of **6** as an off-white solid, mp 132–133 °C. Anal. ($C_{16}H_{15}NO_3$) C, H, N.

A solution of PCl_3 (2.04 g, 14.9 mmol) in toluene (10 mL) was added dropwise to a suspension of the above acid (12.0 g, 44.6 mmol) in toluene (75 mL) at room temperature under N_2. The resulting mixture was stirred at reflux for 2 h, allowed to cool, and then quenched by first adding 10% aqueous Na_2CO_3 (100 mL) and then stirring vigorously for 10 min. The volatiles were removed in vacuo, and the aqueous residue was extracted with EtOAc. The organic layer was washed with NaOH, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting solid was triturated with EtOAc/hexanes and collected by suction filtration to provide an off-white solid. This material was triturated with hot MeOH/EtOAc, allowed to cool, and then collected by suction filtration to yield 7.22 g of **9** as a white solid, mp 174.5–175 °C. Anal. ($C_{22}H_{18}N_2O$) C, H, N.

2-(3-Phenylpropyl)-3-phenyl-4(3*H*)-quinazolinone Hydrochloride (10). A solution of 4-phenylbutyric acid (5.0 g, 30 mmol), thionyl chloride (7.2 g, 60 mmol), and 2 drops of DMF was stirred at reflux. After 4 h, excess thionyl chloride was removed under reduced pressure. The resulting oily residue was dissolved in CH_2Cl_2 (20 mL) and cautiously (exothermic reaction) added to a solution of methyl anthranilate (4.6 g, 30 mmol), pyridine (2.6 g, 33 mmol), and CH_2Cl_2 (50 mL). After stirring for 30 min, the reaction mixture was quenched with H_2O. The separated organic layer was washed with 1 N HCl and 1 N NaOH, dried over $MgSO_4$, and concentrated under reduced pressure to give 8.86 g of the intermediate ester as an oil. This material (5.0 g, 17 mmol) was saponified and isolated as described above to give 4.65 g of crude acid. Recrystallization from EtOAc provided 2.6 g of **7** as a white solid, mp 137–138 °C. Anal. ($C_{17}H_{17}NO_3$) C, H, N.

In a fashion analogous to compound 8 the above acid (12.0 g, 42.4 mmol) was converted to 7.1 g of **10**, mp 161–193 °C. Anal. ($C_{23}H_{21}N_2OCl$) C, H, N.

2-(1*H*-Indol-3-ylmethyl)-3-phenyl-4(3*H*)-quinazolinone (15). Solid 1,1′-carbonyldiimidazole (5.4 g, 33 mmol) was added to a solution of 3-indoleacetic acid (5.79 g, 33.1 mmol) in THF (100 mL) at room temperature. After stirring under N_2 for 15 min, methyl anthranilate (5.0 g, 33 mmol) and pyridinium *p*-toluenesulfonate (20.0 g, 80 mmol) were added. The reaction mixture was stirred at reflux for 24 h, cooled, and concentrated in vacuo. The residue was partitioned between 1 N HCl and EtOAc and heated until two clear layers were obtained. The aqueous layer was removed and the organic layer was allowed to cool, washed with H_2O, 1 N NaOH, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting product was triturated with EtOAc/hexanes and collected by suction filtration to give 8.85 g of 2-(3-indolyl)-*N*-[2-(methoxycarbonyl)phenyl]acetamide as a pale yellow granular solid that was saponified with 1 N NaOH (32 mL) in refluxing MeOH (100 mL). After 30 min the reaction mixture was cooled, concentrated in vacuo, acidified with 1 N HCl (40 mL), and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Trituration with EtOAc/hexanes provided 8.0 g of **12** as an off-white solid, mp 205–207 °C. Anal. ($C_{17}H_{14}N_2O_3$) C, H, N.

To a solution of the above product (7.0 g, 23.8 mmol) in THF (100 mL) at room temperature was added 1,1′-carbonyldiimidazole (4.24 g, 26.2 mmol). After stirring for 30 min, aniline (2.4 mL, 26 mmol) and pyridinium *p*-toluenesulfonate (15.8 g, 63 mmol) were added. The reaction mixture was stirred at reflux under N_2 for 48 h, cooled, and concentrated in vacuo. The residue was partitioned between EtOAc and 1 N HCl. The organic phase (which contained an undissolved solid) was washed once with 1 N HCl and three times with H_2O. The organic phase was separated and concentrated in vacuo. The residue was taken up in toluene and again concentrated. The resulting solid was triturated with EtOAc/hexanes and collected by vacuum filtration. The product was then dispersed in MeOH/EtOAc, heated to boiling, allowed to cool, and collected by suction filtration to afford 3.08 g of the intermediate 2-(3-indolyl)-*N*-[2-(anilinocarbonyl)phenyl]acetamide as white needles, mp 235–236.5 °C. Anal. ($C_{23}H_{19}N_3O_2$) C, H, N.

A mixture of the above product (500 mg) and *p*-toluenesulfonic acid (26 mg) in toluene (20 mL) was heated to reflux under a drying tube with azeotropic removal of water for 3 h. Additional *p*-toluenesulfonic acid (26 mg) was added to the reaction mixture and heating was continued for an additional 21 h. The mixture was cooled, diluted with EtOAc, washed (saturated aqueous $NaHCO_3$ and brine), dried over Na_2SO_4, and concentrated in vacuo. The residue was triturated with MeOH/EtOAc and filtered. The filtrate was concentrated in vacuo and chromatographed (50% EtOAc/hexanes, SiO_2) to give **15** as a yellow oil that crystallized from EtOAc/hexanes as fine white needles (150 mg), mp 191–192 °C. Anal. ($C_{23}H_{17}N_3O$) C, H, N.

2-[2-(1*H*-Indol-3-yl)ethyl]-3-phenyl-4(3*H*)-quinazolinone (2). In a fashion analogous to compound **12**, 3-(3-indolyl)propionic acid (6.0 g, 32 mmol) and methyl anthranilate (4.79 g, 32 mmol) was converted to 6.34 g (92% yield) of 3-(3-indolyl)-*N*-(2-carboxyphenyl)propionamide (**13**) as an off-white, granular solid, mp 197–199 °C. Anal. ($C_{18}H_{16}N_2O_3$), C, H, N.

To a solution of the above acid (6.20 g, 20 mmol) in THF (50 mL) at room temperature was added 1,1′-carbonyldiimidazole (3.26 g, 20 mmol). The reaction was stirred under a dry atmosphere for 30 min after which time aniline (2 mL, 22 mmol) and pyridinium *p*-toluenesulfonate (4.03 g, 16 mmol) were added. The resulting reaction mixture was stirred at reflux for 48 h, allowed to cool, and concentrated under reduced pressure. The product was taken up in EtOAc and washed with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, and brine and dried over Na_2SO_4. Solvent removal afforded a brown oil that crystallized from EtOAc/hexanes. Recrystallization from MeOH/EtOAc furnished 2.28 g of **2** as white fluffy needles, mp 193–194 °C. Anal. ($C_{24}H_{19}N_3O$) C, H, N.

2-[3-(1*H*-Indol-3-yl)propyl]-3-phenyl-4(3*H*)-quinazolinone (16). In a fashion analogous to compound **2**, methyl anthranilate (5.00 g, 33.1 mmol) and 3-indolebutyric acid (6.72 g, 33.1 mmol) furnished 1.64 g (12% overall yield for three steps) of **16**, mp 202–204 °C. Anal. ($C_{25}H_{21}N_3O$) C, H, N.

2-[2-(1*H*-Indol-3-yl)-1-methylethyl]-3-[3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone (19). To a solution of 2-methyl-3-indolepropionic acid[17] in CH_2Cl_2 (50 mL) was added 1,1′-carbonyldiimidazole (3.5 g, 22 mmol) portionwise. After stirring at room temperature for 30 min, 2-amino-*N*-(3-isopropoxyphenyl)benzamide[4] (**17**) (5.3 g, 20 mmol) was added and the reaction mixture was stirred at reflux for 48 h. Solvent removal in vacuo and chromatography (Prep 500, SiO_2, gradient elution: 20% EtOAc/hexanes to 30% EtOAc/hexanes) provided 2.01 g of the intermediate **18** as a white solid. This material was stirred with pyridinium *p*-toluenesulfonate (2.1 g, 8.4 mmol) in refluxing pyridine (10 mL) for 20 h. Solvent removal and chromatography (Prep 500, SiO_2, 20% EtOAc/hexanes) afforded 1.3 g of white solid. Recrystallization from EtOAc provided 1.04 g of **19** as colorless crystals, mp 186–190 °C. Anal. ($C_{28}H_{27}N_3O_2$) C, H, N.

2-[2-(1*H*-Indol-3-yl)ethyl]-3-[3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone (22). A mixture of 5-(indol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[18] (**20**) (97.3 g, 360 mmol), 2-amino-*N*-(3-isopropoxyphenyl)benzamide[4] (**17**) (96.3 g, 360 mmol), pyridinium *p*-toluenesulfonate (45.2 g, 180 mmol), and pyridine (400 mL) was stirred at reflux under N_2 for 48 h.

The reaction mixture was cooled, concentrated under reduced pressure, and chromatographed in three lots (Prep 500, SiO_2, gradient elution: 10% EtOAc/hexanes to 20% EtOAc/hexanes) to give 74.3 g of combined crude product. A 70.3-g amount of this material was dissolved in warm EtOAc and HCl gas was passed over the solution. The precipitated solid was collected by suction filtration, washed with EtOAc, and then partitioned between 1 N NaOH and CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting oil was crystallized from EtOAc to afford 49.6 g of **22**, mp 165–166 °C. Anal. ($C_{27}H_{25}N_3O_2$) C, H, N.

2-[2-(1*H*-Indol-3-yl)propyl]-3-[3-(1-methylethoxy)-phenyl]-4(3*H*)-quinazolinone Hydrochloride (23). A mixture of indole (10 g, 85 mmol), Meldrum's acid (12.3 g, 85 mmol), acetaldehyde (7.52 g, 171 mmol), proline (0.5 g), and MeCN (50 mL) was heated in an oil bath maintained at 35–40 °C for 2 h. The solvent was removed under reduced pressure and the resulting oily residue was chromatographed (Prep 500, SiO_2, 15% EtOAc/hexanes) to give 17 g of **21** as a yellow solid (69%).

A mixture of the above product (2.9 g, 10 mmol), 2-amino-*N*-(3-isopropoxyphenyl)benzamide[4] (**17**) (2.7 g, 10 mmol), pyridinium *p*-toluenesulfonate (1.3 g, 5 mmol), and pyridine (20 mL) was stirred at reflux for 48 h. The reaction mixture was cooled, concentrated under reduced pressure, and partitioned between EtOAc and H_2O. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. Solvent removal and column chromatography (SiO_2, gradient elution: 10% EtOAc/hexanes, 15% EtOAc/hexanes, 20% EtOAc/hexanes and finally 30% EtOAc/hexanes) gave 2.66 g of the desired product as an oil. The HCl salt was formed by passing HCl gas over an EtOAc solution of the free base. The resulting crystals were collected and washed with EtOAc to provide 1.7 g of **23** (36%), mp 199–203 °C. Anal. ($C_{28}H_{28}N_3O_2Cl$) C, H, N.

(*E*)-2-[2-(1*H*-Indol-3-yl)ethenyl]-3-[3-(1-methylethoxy)-phenyl]-4(3*H*)-quinazolinone (26). A mixture of 2-amino-*N*-(3-isopropoxyphenyl)benzamide[4] (**17**) (10.5 g, 38.7 mmol), acetoacetone (3.9 g, 38.7 mmol), and concentrated HCl (13 mL) in absolute EtOH (100 mL) was stirred at reflux for 1 h. After cooling to room temperature, the volatiles were removed under reduced pressure, and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to provide 3-[3-(1-methylethoxy)phenyl]-2-methyl-4(3*H*)-quinazolinone (**24**) as an oil that solidified upon standing.

A mixture of the above product (2.0 g, 6.8 mmol) and indole-3-carboxaldehyde (2.0 g, 13.8 mmol) in DMF (0.5 mL) was heated in a 180 °C oil bath for 20 h under N_2. The reaction mixture was cooled, MeOH was added, and the resulting yellow solid was collected by suction filtration and then rinsed with MeOH and Et_2O to furnish 1.66 g of crude product. Recrystallization from THF/MeOH provided 1.39 g of **26**, mp 244–245 °C. Anal. ($C_{27}H_{23}N_3O_2$) C, H, N.

(*E*)-2-[2-(5-Bromo-1*H*-indol-3-yl)ethenyl]-3-[3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone (27). $POCl_3$ (21.5 g, 140 mmol) was added dropwise to DMF (40.9 g, 560 mmol) at 10 °C under N_2 while the temperature of the reaction mixture was maintained between 10 and 20 °C. A solution of 5-bromoindole (25 g, 130 mmol) in DMF (25 mL) was subsequently added dropwise and the resulting mixture was stirred for 30 min. Additional DMF (30 mL) was added and the stirring was continued for 30 min. The reaction was quenched by cautiously adding cracked ice, NaOH (20 g), and EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting solid residue was suspended in a small amount of EtOAc and collected by suction filtration to give 20.9 g of 5-bromoindole-2-carboxaldehyde that was sufficiently pure for the next reaction.

In a fashion analogous to **26**, the indole prepared above (2.0 g, 6.8 mmol) and 3-[3-(1-methylethoxy)phenyl]-2-methyl-4-(3*H*)-quinazolinone (**24**) (2.0 g, 7.2 mmol) was converted to 1.5 g of compound **27** as a yellow solid after recrystallization from THF/MeOH, mp 315–316 °C. Anal. ($C_{27}H_{22}N_3O_2Br$) C, H, N.

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Supplementary Material Available: Atomic coordinates, bond lengths, bond angles, and anisotropic temperature factors for compounds **2**, **19**, and **22** (13 pages). Ordering information is given on any current masthead page.