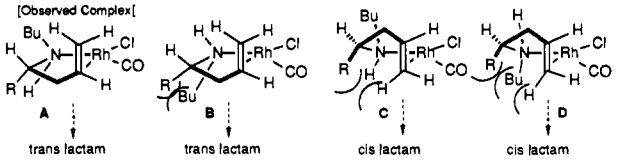
Scheme I



alkene hydrocarboxylation is a highly diastereofacially selective process due to the selectivity inherent in the ligand exchange process and the syn nature of the hydrometalation. Further studies are in progress, and these results will be reported in due course.

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Supplementary Material Available: Listings of spectral data for Rh(I) complexes **3–7** and **9** and lactams **11–13** and **16** (9 pages). Ordering information is given on any current masthead page.

Nonpeptidal Peptidomimetics with a β-D-Glucose Scaffolding. A Partial Somatostatin Agonist Bearing a Close Structural Relationship to a Potent, Selective Substance P Antagonist

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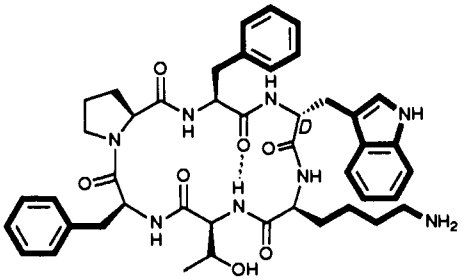
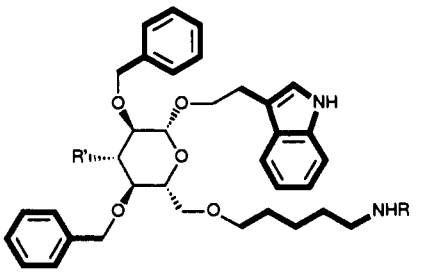
We report herein that the use of β-D-glucose as a scaffold for the synthesis of nonpeptidal peptidomimetics[1] has revealed three noteworthy findings: (1) a designed nonpeptidal peptidomimetic is recognized by its receptor at low concentrations as an agonist; (2) at higher concentrations this compound becomes the first known antagonist of somatostatin (SRIF); and (3) a completely unexpected change in biological profile results from a seemingly minor structural modification.

The design and synthesis of β-D-glucose-based nonpeptide mimetics of the potent cyclic hexapeptide SRIF agonist (I)[2,3] were previously reported.[4] It was found that II and III completely displaced [^{125}I]-CGP 23996 from SRIF receptors on membranes from cerebral cortex, pituitary, and AtT-20 cells with IC_{50}'s of 10 and 1.3 μM, respectively.[5] Sugars II and III also bound weakly to the β_2-adrenergic receptor. Subsequent analysis has now shown that III is a β_2-adrenergic antagonist with an IC_{50} of 3 μM.



I (L-363,301)



II R = H, R' = OBn
III R = R = H
IV R = Ac, R' = OBn

We now report the striking observation that in a functional assay III inhibits GRF-induced growth hormone (GH) release by cultured rat anterior pituitary cells[6] with an IC_{50} of 3 μM, i.e., III is an SRIF agonist at its endocrine receptor. That III can act as an SRIF agonist strongly suggests that the binding is specific and that the SRIF receptor recognizes the designed III as an SRIF mimetic. This agonism runs counter to the prevailing opinion that designed peptidomimetics with novel scaffolding are unlikely to achieve the degree of fit at the endocrine receptor required for agonism.[7] The maximal level of inhibition (found at 50 μM) was only about half that seen with an optimal level of SRIF, suggesting that III is a partial agonist. Indeed at higher concentrations, III antagonized SRIF-induced receptor activation. That III is the first compound, peptidal or nonpeptidal, to display a long-sought antagonism at the SRIF receptor is at least as noteworthy as the above agonism.

We have now found that II and III display a higher affinity to the substance P (SP) receptor, with IC_{50}'s of 0.12 and 0.18 μM, respectively. Remarkably, the *N*-acetyl derivative IV[9] binds to

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the SP receptor with an IC_{50} of 60 nM. In a functional assay it inhibited SP-mediated inositol phosphate production.[10] Further, IV is highly selective for the substance P receptor and does not interact with some 50 other receptors, including the SRIF and β-adrenergic receptors at concentrations of 1 μM.[11] That such a subtle modification can produce this switch in binding affinity is surprising; in addition, IV is to our knowledge the first neutral SP antagonist.[12]

It is of interest that the SRIF, β-adrenergic, and SP receptors utilize G-protein-mediated signal transduction. Such receptors share structural as well as functional similarities characterized by seven hydrophobic transmembrane domains connected by hydrophilic extramembranous loops.[13,14] The interaction of II and III with three different G-protein-coupled receptors, as well as the highly lipophilic nature of these glycosides, suggests that the binding may involve similar interactions within the conserved hydrophobic domains of the three receptors.[15] The high affinity and selectivity of IV for the SP receptor must reflect some specific interactions of the compound with a binding domain of that receptor. While a structural relationship between SP and IV is not obvious, it is tempting to speculate that the benzyl substituents on the glucose scaffold might be binding to the site in the receptor normally occupied by the two phenylalanine residues near the C-terminus of substance P and/or one or more of the three phenyl groups of CP-96,345[16] or RP6758,[17] both substance P antagonists.

Ariëns had previously called attention to the importance in receptor binding of hydrophobic double ring systems.[18] More recently, Tanford[19] and Wiley and Rich[20] have discussed the interactions whereby hydrophobic peptides and other flexible hydrophobic organic molecules assume a stabilized conformation in aqueous medium, a phenomenon which Rich termed hydrophobic collapse. This may play a role in the high affinity of IV for the substance P receptor.

In summary, we have observed that β-D-glucose can serve as a scaffold for molecules that can bind to G-protein-coupled receptors. The unexpected observation that compounds designed to act at the somatostatin receptor are also antagonists of the β-adrenergic and substance P receptors underscores the structural similarities in the binding domains of the family of G-protein-coupled receptors. That the seemingly subtle structural differences between II and IV produced such a dramatic change in biological profile was completely unexpected, and it suggests the possibility that agonists and antagonists of other G-protein-linked receptors can be found by the strategy described herein. Further work to design high-affinity ligands around the β-D-glucose template are underway.

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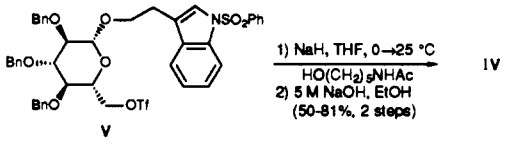
(8) A peptide which blocked the in vivo effects of somatostatin on GH release (Fries, J. L.; Murphy, W. A.; Sueras-Diaz, J.; Coy, D. A. *Peptides* **1982**, *3*, 811) was subsequently found to involve receptors other than the pituitary somatostatin receptor (Coy, D. A. Personal communication to R.H.).

(9) The synthesis of the novel IV unexpectedly could not be accomplished via acetylation of II due to partial indole acylation giving gross mixtures even with a stoichiometric amount of acetic anhydride. This is in contrast to the fact that the solid-phase peptide synthesis of Trp-containing peptides does not require deactivation of the indole heterocyclic ring and that I was selectively acetylated on the primary amine. IV was prepared as shown.



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(11) We are indebted to Drs. L. Iversen and S. Freedman (Merck Research Laboratories, Terlings Park, Harlow, UK) and Dr. D. J. Pettibone (Department of Biomedical Pharmacology, Merck Research Laboratories, West Point, PA) for these results. We are also grateful to the Merck Research Laboratories for making IV available for broad screening at Panlabs, Inc.

(12) Interestingly, the N-acetylated SRIF agonist MK 678[2] c-(*N*-Me-Ala-Tyr-D-Trp-Lys-Val-Phe) does not bind to the SP receptor. Thus nonpeptidal peptidomimetics can disclose structural relationships between receptors not revealed by their peptidal counterparts.

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(15) It seems likely that as we learn more about the similarities between the primary and tertiary structures of diverse receptors, the changes in biological profile resulting from seemingly minor alterations in molecular structure of small molecules [e.g., valium → tifluadom (Römer, D.; Büscher, H. H.; Hill, R. C.; Maurer, R.; Petcher, T. J.; Zeugner, H.; Benson, W.; Finner, E.; Milkowski, W.; Thies, P. W. *Nature* **1982**, *298*, 759)] will become more understandable [Hirschmann, R. Review of the Fogarty International Center Conference, NIH: Peptides in Health and Disease. *Int. J. Pept. Protein Res.*, in press].

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On the Origins of the DNA Sequence Selectivity of Mitomycin Monoalkylation Transformations

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The cytotoxicity and antitumor activity of mitomycin C (**1a**), a clinically important anticancer agent,[1] have been associated with the DNA–drug bonding process.[2] UVRABC nuclease assay on mitomycin C–DNA monoadduct sites revealed that DNA modification occurred predominantly at 5′CG* sequences (G*, site of drug lesion) and that 5′CG*G sequences were the preferred trinucleotide units for monoalkylation transformations.[3] Analysis of the data and computer-aided model building studies indicated that two key hydrogen bonds contributed to the sequence selectivity.[3b] We have proposed that both the C(10) oxygen of the carbamate group[4] and the N(2) ammonium group in the activated mitomycin species (**2a**) are well-situated to hydrogen bond to the

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