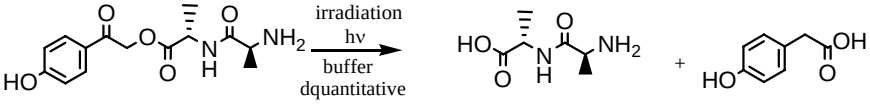
Rapid, Controlled Release of Neurotransmitters, Nucleotides and Other Bioactive Substrates

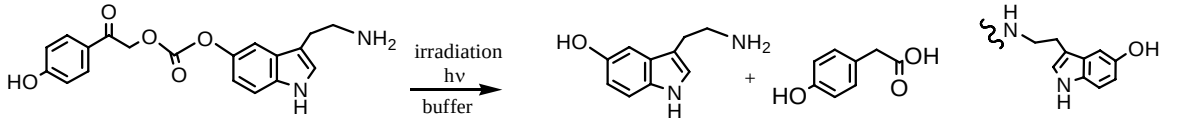
Richard S. Givens, Professor, Organic Division

The controlled release of neurotransmitters and other peptide and protein substrates can be employed to study their biological action both *in vitro* and *in vivo*. The most powerful means to effect controlled release is through photochemistry permitting the regulation of the temporal and spatial release along with the concentration of the protein or peptide substrate.[1] This is possible by use of flash lamps or pulsed lasers, focusing the light on only those regions of the biological tissue to be studied and changing the intensity of the light source, respectively. To gain the maximum utility of this approach, it is essential that chemists develop photoactive removable groups that can be covalently attached to a peptide or an agonist/antagonist substrate that upon irradiation rapidly release the substrate. We have already accomplished this feat for nucleotides[2], amino acids, certain peptides[3] and a selected group of neuroactive substrates. We are now applying this approach to other classes of biologically active agents.



1 **2** **3** equation 1

Our results[4] with Ala-Ala (eq. 1) and with Bradykinin, a pain transducer and agonist for glial cells, have shown that the approach is very valuable for studying cell responses to natural and unnatural stimulants[5]. We have synthesized O-(4'-hydroxyphenacyl) Ala Ala (**1**) and shown that the dipeptide **2** is released upon photolysis in quantitative yield. This model serves as the basis for our more general study of other amino acids, peptides and neurotransmitters. The REU researcher will learn to work with neurotransmitters to synthesize the protected agonist using standard organic synthetic methods and will conduct original research on synthesis, spectroscopic identification, and photorelease of the *p*-hydroxyphenacyl serotonin or dopamine (eq. 2).



4, pHP carbonate protected seratonin $-CO_2$ **5**, seratonin **3** also, N protected

equation 2

References:

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2. Givens, R. S.; Athey, P. S.; Kueper, L. W., III (an NSF REU participant); Matuszewski, B.; Xue, J.-y., Fister, T. (an NSF REU participant)*J. Am. Chem. Soc.* **1993,** *115*, 6001-6010;. b) Park, C-H.; Givens, R. S. *Tetrahedron* Letts, **1996**, *37*, 6259-6262. c) *ibid.*, *J. Am. Chem. Soc.* **1997,** 119, 2453-2463.
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5. For representative examples, see: Goeldner, M; Givens, R. S. "Dynamic Studies in Biology: Phototriggers, Photoswitches, and Caged Molecules, Wiley Verlag GmbH & Co.Weinheim.