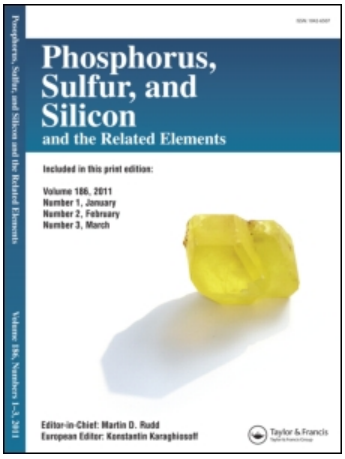


## Phosphorus, Sulfur, and Silicon and the Related Elements
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# Anti-Cocaine Catalytic Antibodies

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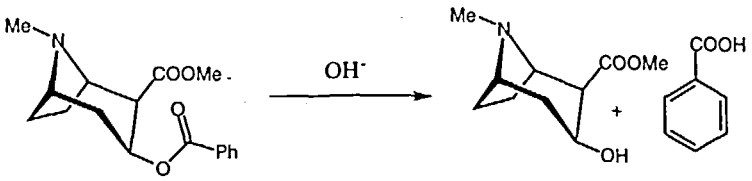
Over 50,000,000 Americans have used cocaine (**1**) since 1980 and approximately 2,000,000 are presently addicted with disastrous medical and social consequences.[1] At present, no efficient drug therapy is available for the management of cocaine abuse and dependence. Cocaine is hypothesized to exert its addictive effect by blocking a transport protein for the neurotransmitter dopamine, and the difficulties inherent in blocking a blocker may in part explain the failure to develop a useful therapeutic agent. One alternative to the classical receptor antagonist approach would be a circulating catalytic antibody that could degrade cocaine and interfere with the delivery of the drug to the central nervous system. To obtain antibodies able to catalyze the hydrolysis of cocaine to the inactive products, ecgonine methyl ester (**2**) and benzoic acid (**3**), we synthesized a series of stable phosphonate monoester transition state analogs for benzoyl esterolysis (**4a-c**). With these immunogens we elicited the first artificial enzymes able to degrade cocaine *in vitro*.[2,3]

The most active catalytic antibody, Mab 15A10,[3] displayed a hydrolysis rate acceleration of $2.4 \times 10^4$, a turnover rate of 2 $min^{-1}$ and a Km of 220 μM. These parameters were sufficient to commence preclinical studies in animal models of addiction and overdose.[4] In a model of cocaine overdose, this antibody protected rats from the lethal effects of cocaine, while in a comparative study, a non-catalytic cocaine-binding antibody did not reduce cocaine toxicity.

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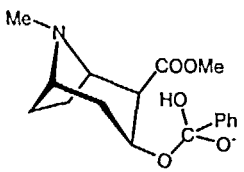


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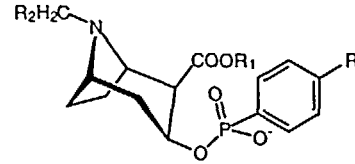


**4a: $R_1$=spacer**
**4b: $R_2$=spacer**
**4c: $R_3$=spacer**



Consistent with catalytic degradation, the concentration of ecgonine methyl ester was increased tenfold in the plasma of rats that simultaneously received Mab 15A10 and cocaine. Also, in a rat model of cocaine addiction, Mab 15A10 blocked completely and specifically the reinforcing effect of cocaine. A humanized version of Mab 15A10 will allow evaluation of this approach in a primate self-administration model as a prelude to clinical trials.

Our effort to improve the activity of the first artificial enzymes to degrade cocaine is focused on the synthesis of novel transition-state analogs, the mutagenesis of our most active antibody, and the development of high throughput screening assays for the cocaine esterase activity.

**Acknowledgments**

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## *References*

[1] The National Drug Control Strategy, Office of the National Drug Control Policy, Executive Office of the President of the United States, Washington (1996), p. 41.

[2] D. W. Landry, K. Zhao, G. X. Yang, M. Glickman, T. M. Georgiadis, *Science*, **259**, 1899 (1993).

[3] G. X. Yang, J. Chun, H. Arakawa-Uramoto, X. Wang, M.A. Gawinowicz, K. Zhao, D. W. Landry, *J. Am. Chem. Soc.*, **118**, 5881 (1996).

[4] B. Mets, G. Winger, C. Cabrera, S. Seo, S. Jamdar, G. W. Yang, K. Zhao, J. R. Briscoe, R. E. Almonte, J. H. Woods, D. W. Landry, *Proc. Nat. Ac. Sci.*, in press (1998).