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To the memory of my grandparents-
Henry and Louise Heymann & Reber and Thelma Dixon

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Abstract

MOLECULAR RECOGNITION SMALL MOLECULES BY RHO-ASSOCIATED KINASE

by

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Rho-associated coiled-coil containing protein kinase (or ROCK) is the first known effector of the Rho GTPase family of proteins, which are responsible for processes such as adhesion, motility, proliferation, differentiation, and apoptosis. ROCK is one of the six clinically-validated kinase drug targets and its inhibition has been suggested as a potential therapeutic mode of action to treat a diverse array of diseases including cancer and autoimmunity. **BZD-29** is a 1,4-benzodiazepine-2,5-dione with demonstrated attenuation of disease in the *Schistosoma mansoni* model of pulmonary inflammation and no general toxicity in rodents. Target identification and validation along with mechanism of action studies have demonstrated that **BZD-29** is an ATP-competitive inhibitor of ROCKII. Although high resolution crystal structures exist for both of the two known ROCK isoforms, the molecular contacts necessary for potency and selectivity among the ROCK enzymes remain a topic of research and debate. This thesis describes the design, synthesis, and analysis of a series of analogs of **BZD-29**,

designed to probe and optimize the structural features important for potent inhibition and selectivity for ROCKII. These efforts have resulted in the development of a highly stereoselective synthetic route for the production of chiral 1,4-benzodiazepine-2,5-diones, the design of inhibitors with 110-fold potency over **BZD-29** and 10-fold potency over Fasudil, and the establishment of highly successful structure activity relationship models and computational models for use in future analog design.