The polyamines putrescine, spermidine and spermine are ubiquitous polycationic compounds that are found in nearly every cell type, and are required to support a wide variety of cellular functions. The existence of multiple cellular effector sites for naturally occurring polyamines implies that there are numerous targets for polyamine-based therapeutic agents. Through a program aimed at the synthesis and evaluation of biologically active polyamine analogues, our laboratory has identified three distinct structural classes of polyamine derivatives that exhibit promising biological activity in vitro. We have synthesized more than 200 symmetrically- and unsymmetrically substituted alkylpolyamines that possess potent antitumor or antiparasitic activity, depending on their backbone architecture and terminal alkyl substituents. Along similar lines, we have developed novel polyaminoguanidines and polyaminobiguanides that are promising antitrypanosomal agents, and that selectively inhibit oxidative enzymes such as spermine oxidase (SMO) and acetylpolyamine oxidase (APAO). Finally, we recently reported a series of polyamino- hydroxamic acids (PAHAs) and polyaminobenzamides (PABAs) that inhibit histone deacetylases (HDACs), and in some cases are selective for individual HDAC isoforms. In this presentation, the design and characterization of these polyamine analogues as biochemical probes, and as potential therapeutics, will be described