8-NH2-boldine, an antagonist of ?1A and ?1B adrenoceptors without affinity for the ?1D subtype: Structural requirements for aporphines at ?1- adrenoceptor subtypes

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Structure-activity analysis of 21 aporphine derivatives was performed by examining their affinities for cloned human ?1A, ?1B and ?1D adrenoceptors (AR) using membranes prepared from rat-1 fibroblasts stably expressing each ?1-AR subtype. All the compounds tested competed for [125I]-HEAT binding with steep and monophasic curves. The most interesting compound was 8-NH 2-boldine, which retains the selective affinity for ?1A-AR (pKi = 6.37 ± 0.21) vs. ?1B-AR (pKi = 5.53 ± 0.11) exhibited by 1,2,9,10-tetraoxygenated aporphines, but shows low affinity for ?1D-AR (pKi < 2.5). Binding studies on native adrenoceptors present in rat cerebral cortex confirms the results obtained for human cloned ?1-AR subtypes. The compounds selective for the ?1A subtype discriminate two binding sites in rat cerebral cortex confirming a mixed population of ?1A- and ?1B-AR in this tissue. All compounds are more selective as inhibitors of [3H]-prazosin binding than of [3H]-diltiazem binding to rat cerebral cortica