BENZO-SEPARATED XANTHINES AS PHOSPHODIESTERASE INHIBITORS

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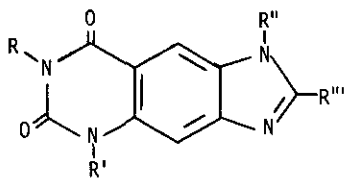
It is now well established that adenosine 3',5'-monophosphate (cAMP) plays a major regulatory role in cellular metabolism and evidence is growing which suggests a similar, less prominent function may exist for guanosine 3',5'-monophosphate (cGMP). A significant component in this regulatory process is the control of the intracellular levels of cAMP and cGMP by, in part, cyclic nucleotide phosphodiesterases which convert the cyclic nucleotides into their 5'-monophosphates. Using pig coronary arteries, Wells and his co-workers have reported (for a leading reference see *J. Med. Chem.* 1981, 24, 954-958) that there are two forms of phosphodiesterase present in this system: (i) a "peak I" calmodulin sensitive form that is considered to be the cGMP phosphodiesterase and (ii) a "peak II" calmodulin insensitive form that only hydrolyzes cAMP. Moderate success in the selective inhibition of the "peak I" or "peak II" forms has been achieved by Wells with appropriately substituted xanthines. In a search for better inhibitor selectivity and to analyze the dimensional limitations for the xanthine derived inhibitors of these two forms, the benzo-separated xanthines (1 and 2) have been prepared and biologically evaluated. In addition to a presentation of these results, progress towards the synthetically more inaccessible analogs represented by 3 will also be summarized.



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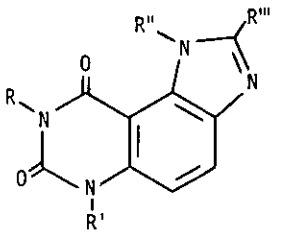

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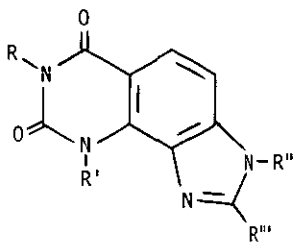

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