Synthesis of 5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-ones: selective antagonists of muscarinic (M3) receptors.

Bradshaw B, Evans P, Fletcher J, Lee AT, Mwashimba PG, Oehlrich D, Thomas EJ, Davies RH, Allen BC, Broadley KJ, Hamrouni A, Escargueil C.

Abstract

Two approaches to tetrahydro-[1H]-2-benzazepin-4-ones of interest as potentially selective, muscarinic (M(3)) receptor antagonists have been developed. Base promoted addition of 2-(tert-butoxycarbonylamino)methyl-1,3-dithiane with 2-(tert-butyldimethylsiloxymethyl)benzyl chloride gave the corresponding 2,2-dialkylated 1,3-dithiane which was taken through to the dithiane derivative of the parent 2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-one by desilylation, oxidation and cyclisation via a reductive amination. After conversion into the N-tert-butyloxycarbonyl, N-toluene p-sulfonyl and N-benzyl derivatives , hydrolysis of the dithiane gave the N-protected tetrahydro-[1H]-2-benzazepin-4-ones . However, preliminary attempts to convert these into 5-cycloalkyl-5-hydroxy derivatives were not successful. In the second approach, ring-closing metathesis was used to prepare 2,3-dihydro-[1H]-2-benzazepines which were hydroxylated and oxidized to give the required 5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-ones. Following preliminary studies, ring-closing metathesis of the dienyl N-(2-nitrophenyl)sulfonamide gave the dihydrobenzazepine which was converted into the 2-butyl-5-cyclobutyl-5-hydroxytetrahydrobenzazepin-4-one by hydroxylation and N-deprotection followed by N-alkylation via reductive amination, and oxidation. This chemistry was then used to prepare the 2-[(N-arylmethyl)aminoalkyl analogues , , and . N-Acylation followed by amide reduction using the borane-tetrahydrofuran complex was also used to achieve N-alkylation of dihydrobenzazepines and this approach was used to prepare the 5-cyclopentyl-5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-one and the 5-cyclobutyl-8-fluoro-5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-one . The structures of 2-tert-butyloxycarbonyl-4,4-propylenedithio-2,3,4,5-tetrahydro-[1H]-2-benzazepine and (4RS,5SR)-2-butyl-5-cyclobutyl-4,5-dihydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepine were confirmed by X-ray diffraction. The racemic 5-cycloalkyl-5-hydroxy-2,3,4,5-tetrahydro-[1H]-2-benzazepin-4-ones were screened for muscarinic receptor antagonism. For M(3) receptors from guinea pig ileum, these compounds had log(10)K(B) values of up to 7.2 with selectivities over M(2) receptors from guinea pig left atria of approximately 40.