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(57) Abstract: The invention relates to novel compounds which are both phosphodiesterase 4 (PDE4) enzyme inhibitors and muscarinic M3 receptor antagonists, methods of preparing such compounds, compositions containing them and therapeutic use thereof. M3 Binding assay: CHO-KI clone cells expressing the human M3- receptor (Swissprot P20309) were harvested in Ca⁺⁺/Mg⁺⁺-free phosphate-buffered saline and collected by centrifugation at 1500 rpm for 3 min. The pellets were resuspended in ice cold buffer A (15 mM Tris-HCl pH 7.4, 2 mM MgCl₂, 0.3 mM EDTA, 1 mM EGTA) and homogenized by a PBI politron (setting 5 for 15 s). The crude membrane fraction was collected by two consecutive centrifugation steps at 40000 g for 20 min at 4°C, separated by a washing step in buffer A. The pellets obtained were finally resuspended in buffer B (75 mM Tris HCl pH 7.4, 12.5mM MgCl₂, 0.3 mM EDTA, 1 mM EGTA, 250 mM sucrose), and aliquots were stored at - 80°C. The day of experiment, frozen membranes were resus- pended in buffer C (50 mM Tris-HCl pH 7.4, 2.5 mM MgCb, 1 mM EDTA). The non selective muscarinic radio ligand [³H]-N- methyl scopolamine(Mol.Pharmacol.45:899-907) was used to label the M3 binding sites. Binding experiments were performed in duplicate (ten point concentrations curves) in 96 well plates at radioligand concentration of 0.1-0.3 nM. The non specific binding was determined in the presence of cold N-methyl scopolamine 10 uM. Samples (final volume 0.75 mL) were incubated at room tem- perature for 90 min. The reaction was terminated by rapid filtration through GF/B Unifilter plates and two washes (0.75 mL) with cold buffer C using a Packard Filtermate Harvester. Radioactivity on the filters was measured by a microplate scintillation counter TriCarb 2500 (PerkinElmer). Representative compounds of the invention, when tested in one of the above reported protocols, dis- played an IC₅₀ lower than 100 nM. Representative compounds of the invention displayed an IC₅₀ lower than 100 nM in both PDE4 cell free and M3 binding assays.

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