Target Name	Muscarinic acetylcholine receptor M3
Target TTD ID	TTDS00004

Target Species	Human
Chemical Type	Quaternary soft anticholinergic structures
Mode of Action	Antagonist
QSAR Model 1	$\mathrm{p}A_2 = 15.115_{(\pm 0.878)} - 0.0260_{(\pm 0.0029)}V - 2.413_{(\pm 0.249)}\mathrm{I\_acid} + 0.980_{(\pm 0.297)}\mathrm{I\_2R} - 0.760_{(\pm 0.182)}\mathrm{I\_PS} + 0.529_{(\pm 0.169)}\mathrm{I\_cPe}$ $n = 43, \quad r^2 = 0.833, \quad q^2_{\mathrm{LO4GO}} = 0.755, \quad \sigma = 0.449, \quad F = 37.0$
QSAR Model 2	$\mathrm{p}K_i\,(\mathrm{M}_3) = 13.946_{(\pm 1.260)} - 0.0201_{(\pm 0.0041)}V - 1.889_{(\pm 0.443)}\mathrm{I\_acid} + 1.340_{(\pm 0.363)}\mathrm{I\_2R} + 1.364_{(\pm 0.317)}\mathrm{I\_PcHC}$ $n = 28, \quad r^2 = 0.687, \quad q^2_{\mathrm{LO4GO}} = 0.493, \quad \sigma = 0.553, \quad F = 12.6$
QSAR Model 3	$\mathrm{p}A_2 = -0.434 \ln[\mathrm{e}^{-a(V-V_0)/0.434} + \mathrm{e}^{b(V-V_0)/0.434}] + c + d_{\mathrm{acid}}\cdot\mathrm{I\_acid} + d_{2\mathrm{R}}\cdot\mathrm{I\_2R} + d_{\mathrm{PS}}\cdot\mathrm{I\_PS} + d_{\mathrm{cPe}}\cdot\mathrm{I\_cPe}$ $a = 0.050_{(\pm 0.007)}, \quad b = 0.025_{(\pm 0.004)}, \quad c = 8.443_{(\pm 0.145)}, \quad V_0 = 264.1_{(\pm 5.2)}$ $d_{\mathrm{acid}} = -1.942_{(\pm 0.317)}, \quad d_{2\mathrm{R}} = 0.848_{(\pm 0.420)}, \quad d_{\mathrm{PS}} = -1.048_{(\pm 0.244)}, \quad d_{\mathrm{cPe}} = 0.254_{(\pm 0.225)}$ $n = 76, \quad r^2 = 0.698, \quad q^2_{\mathrm{LO4GO}} = 0.620, \quad \sigma = 0.631$

QSAR Model 4	$\log K = -0.434 \ln[e^{-a(V-V_0)/0.434} + e^{b(V-V_0)/0.434}] + c + d_{2OH}\cdot I\_2OH + d_{2cHx}\cdot I\_2cHx + d_{COO}\cdot I\_COO + d_{diRng}\cdot I\_diRng$ $a = 0.020_{(\pm 0.001)}, \quad b = 0.012_{(\pm 0.003)}, \quad c = 6.177_{(\pm 0.113)}, \quad V_0 = 255.0_{(\pm 8.8)}$ $d_{2OH} = 1.197_{(\pm 0.083)}, \quad d_{2cHx} = 1.014_{(\pm 0.084)}, \quad d_{COO} = 0.785_{(\pm 0.077)}, \quad d_{diRng} = 0.827_{(\pm 0.140)}$ $n = 128, \quad r^2 = 0.975, \quad q^2_{LO4GO} = 0.967, \quad \sigma = 0.256$
QSAR Model 5	$\log K = 0.784_{(\pm 0.06)}\pi_R - 0.353_{(\pm 0.26)}(\pi_{-N^{\oplus}\equiv})^2 - 0.171_{(\pm 0.24)}(\pi_{-N^{\oplus}\equiv}) + 0.736_{(\pm 0.11)}\mu_R + 2.309_{(\pm 0.27)}n_{OH} + 2.173_{(\pm 0.29)}$ $n = 128, \quad r^2 = 0.924, \quad \sigma = 0.441, \quad F = 7.0$
Molecular Descriptor	Access the following web-servers to compute molecular descriptors: **MoDel** and **e-dragon** Structural features that influence activity, and corresponding indicator variables, I_*str*; were introduced into the model to account for their presence (I_*str* = 1 if *str* is presemt, 0 otherwise) I_acid for the presence of a carboxylic acid (-COOH), I_2R for enantiomerically pure 2*R* isomers, I_PS for succinic analogues where the carboxylic ester is one postion away from the substitution center (R_3 – CH_2COOR vs R_3 = -COOR in the malonic series), and I_cPe for the presence of a cyclopentyl substitution at the 2-position (as in glycopyrrolate). pA_2 activity values for the guines pig ileum assay effective van der Waals molecular volume (V). The I indicator variables denote the presence (1) or absence (0) of the following structural moleties: I_2OH a 2-hydroxy substituent, I_ 2cHx a 2-cyclohexyl substituent, I_COO an ester moety, I_diRng two ring substituents
Reference	Soft Quaternary Anticholinergics: Comprehensive Quantitative Structure-Activity Relationship (QSAR) with a Linearized Biexponential (LinBiExp) Model. *J. Med. Chem*. 2006, 49, 883-891