PYRIDAZINE DERIVATIVES AS NOVEL ACAT INHIBITORS

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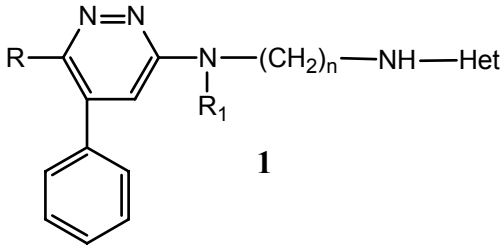
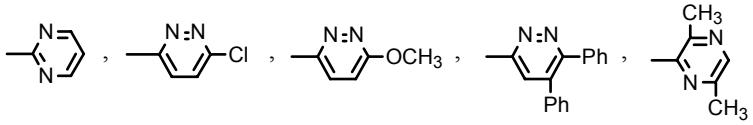
Acyl-CoA:cholesterol acyl transferase (ACAT) is an intracellular enzyme that catalyses the esterification of free cholesterol in various tissues; it represents a good target in the treatment of hypercholesterolemia and coronary disease.
As a part of our ongoing studies on pyridazine derivatives as ACAT inhibitors [1-4] we synthesized a new series of derivatives of general formula **1** :



1

n = 6-8 ; R = H, Ph ; R_1 = H, $(CH_2)_6CH_3$;

Het = 

The present communication describes the synthesis and the pharmacological evaluation of the title derivatives. Their activity was tested toward ACAT extracted from rat liver microsomes. At a final concentration of 100 μg/mL, the most significant compounds showed inhibition ranging between 80 and 95%.

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References:
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[2] Giovannoni, M.P.; Dal Piaz, V.; Kwon, B.-M.; Kim, Y.-K.; Toma, L.; Barlocco, D.; Bernini, F.; Canavesi, M.; *J. Med. Chem.*, **2001**, *44*, 4292-4295
[3] Toma, L.; Giovannoni, M.P.; Dal Piaz, V.; Kwon, B.-M.; Kim, Y.-K.; Gelain, A.; Barlocco, D.; *Heterocycles*, **2002**, *57*, 39-46
[4] Toma, L.; Giovannoni, M.P.; Vergelli, C.; Dal Piaz, V.; Kwon, B.-M.; Kim, Y.-K.; Gelain, A.; Barlocco, D.; *Arc. Pharm. Pharm. Med. Chem.*, **2002**, *11*, 563-566