NOVEL 5-VINYL-3(2H)PYRIDAZINONES AS ORALLY ACTIVE ANTINOCICEPTIVE AGENTS

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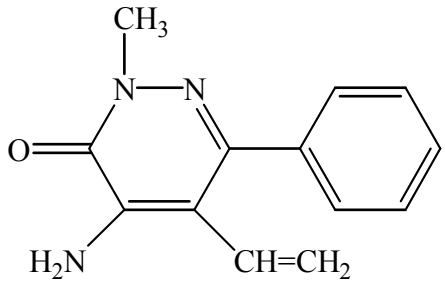
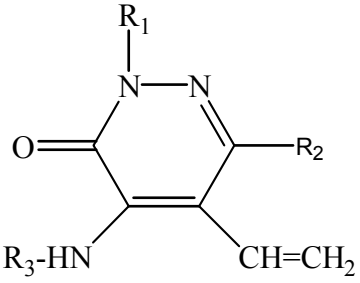
Two major groups of drugs are currently used for treatment of pain: non-steroidal antiinflammatory drugs (NSAIDs) and opioids. The first class shows side-effects like ulcerations, nephrotoxicity and platelet aggregation inhibition. Unwanted effects associated with the clinical use of opioids are: respiratory depression, tolerance, physical dependence and constipation. Thus, there is still the need to discover new pain-killers characterized by higher therapeutic index, in particular for treatment of neuropathic pain.
Pursuing our studies in the field of 4,5-functionalized pyridazinones as antinociceptive agents [1-4] we report here the synthesis of a novel series of compounds (1) structurally related to BB3 [1,2].



BB3



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In the attempt to optimize the potency and the safety of the lead compound BB3, we introduced different alkyl chain at R_1, substituted phenyls and heteroaromatics at R_2 and alkyl(acyl) groups at R_3. The novel compounds were evaluated as antinociceptive agents both in writhing and in hot-plate tests by oral administration. Compound with R_1= n.butyl, R_2= Ph and R_3= Me, as well as the analog with R_1= Me, R_2= 4-pyridyl and R_3= H were the most interesting being able to reduce the writhes of 40% at the dose of 20 mg/kg p.o. and to induce a licking latency of 90-100% at the same dose in the hot-plate test.
SAR studies will be discussed in the occasion of the meeting.

References:
[1] Dal Piaz V., Giovannoni M.P. et al., *Eur. J. Med. Chem*., **1996**, 31, 65-70.
[2] Pieretti S., Dal Piaz V., Giovannoni M.P. et al., *Life Sci*., **1999**, 65, 1381-1394.
[3] Dal Piaz V., Vergelli C., Giovannoni M.P. et al., *Il Farmaco*, **2003**, 58, 1063-1071.
[4] Giovannoni M.P., Vergelli C., Ghelardini C., Dal Piaz V. et al., *J. Med. Chem*. **2003**, 46, 1055-1059.