Pharmacological Reports
2011, 63, 476–486
ISSN 1734-1140

Structure-cardiovascular activity relationships in a group of new 8-alkylamino-1,3-dimethyl-7-(2-hydroxy-3-aminopropyl)-3,7-dihydro-1H-purine-2,6-diones

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Abstract:
On the basis of our earlier studies in a group of 7,8-disubstituted derivatives of 1,3-dimetyl-3,7-dihydropurine-2,6-dione, a series of new 8-alkylamino-1,3-dimethyl-7-(2-hydroxy-3-aminopropyl)-3,7-dihydropurine-2,6-diones (**8-15**) were synthesized and tested for their electrocardiographic, antiarrhythmic and hypotensive activity and for α_1- and α_2-adrenoreceptor affinities. Among the new derivatives, compounds with the 7-[2-hydroxy-3-(4-phenylpiperazine)-propyl] substituent (**9-11**) displayed prophylactic antiarrhythmic activity in epinephrine-induced arrhythmia. Analogue **10** with the 8-(2-morpholin-4-yl)-ethylamino group was the most active (ED_{50} = 3.9 mg/kg and TI = 59.8), which may indicate that this substituent is preferably important for the antiarrhythmic effect. Only compound **11** with the 8-(2-diethylamino)-ethylamino group significantly decreased the systolic (20.4–28.1%) and diastolic (23.4–33.2%) pressure, but this effect lasted for only 1–5 min. The pharmacologically active compounds **9–11** with the phenylpiperazine moiety showed affinity for α_1-receptors (K_i = 0.143–0.383 μM), but the other compounds were almost (**12**–**15**) or completely (**8**) inactive at this site. Compounds **9–11** and **13–15** displayed moderate to low affinity for α_2-receptors (K_i = 0.36–2.7 μM).

Key words:
purine-2,6-diones, antiarrhythmics, hypotensive agents, α_1- and α_2-receptor ligands