SEARCH FOR NEW SCAFFOLD OF THIAZIDES-LIKE DIURETICS

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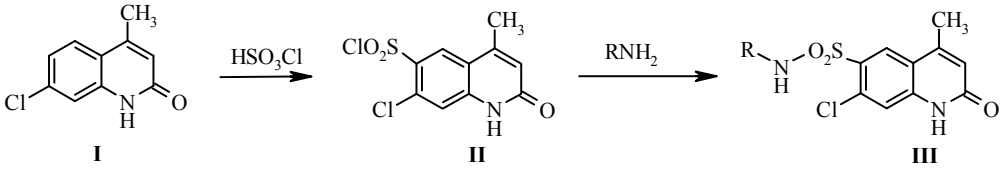
Thiazide and thiazide-like diuretics have formed the cornerstone of the management of hypertension for several decades. They are optional first-line antihypertensive agents for people aged 55 years or older, their effects are seen at low doses but still have metabolic side-effects. Therefore, the discovery of new effective and safe thiazide-like diuretic drugs represents a challenging goal for a research area.

We have supposed that sulfonamides III that have similar structure with hydrochlorothiazide would also have diuretic activity. And it has been successfully confirmed in our previous work for derivatives with aliphatic substituents (III, R=Alk). So the purpose of this work was to synthesize a series of new quinoline-2-ones with sulfonamide moiety bearing different aromatic substituents (I, R=Ar) and study their diuretic activity.

Synthesis of target sulfonamides is shown on scheme:



I **II** **III**

According to the obtained pharmacological data these compounds acted similar to hydrochlorothiazide in the experiment in rats. Among tested compounds 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonic acid anilide (III, R=Ph) has shown the most significant diuretic activity. From the structure–activity point of view, it was found that any substitution, especially in case of *o*-position, in the benzoic ring of sulfonarylamides reduces diuretic activity of synthesized compounds.

Aso sodium, potassium, chlorides and creatinine content in urine and serum of rats also has been measured for synthesized compounds. In all cases increased diuresis was provided mostly due to Na^+ excretion and Na^+/K^+ ratio was more favourable for new compounds then that of hydrochlorothiazide. Determination of acute toxicity of the most active compound (III, R=Ph) in mice (per os) has shown that LD_{50} is more than 10000 mg/kg. That looks promising because LD_{50} of hydrochlorothiazide is about 3000 mg/kg (per os).

Thus, 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonic acid anilide could be considered as a lead compound from this series of new sulfonamides that deserves further investigation, in particular as hypotensive agent.